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RESEARCH**

APPLICATION NUMBER:

208471Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	208471
Submission Date(s):	July 27, 2015
Brand Name	(b) (4)
Generic Name	Lixisenatide injection
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Sanofi-aventis U.S. LLC
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	Prefilled solution for subcutaneous injection: • 10-µg/dose • 20 µg/dose
Proposed Indication	• Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Dosage & Administration	• Administer once daily within one hour prior to (b) (4) the first meal of the day (b) (4) • Inject subcutaneously in the abdomen, thigh or upper arm. • Initiate at 10 mcg once daily for 2 weeks. After 2 weeks, increase the dose to 20 mcg once daily.
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1 Executive Summary

Lixisenatide is being developed by Sanofi. Lixisenatide is a short-acting GLP-1 receptor agonist with affinity for the GLP-1 receptor, has structural similarities to exendin-4 and is claimed to be resistant to enzymatic cleavage by DPP-4. An NDA for lixisenatide was originally submitted on 20 December 2012 but was subsequently withdrawn on 10 September 2013 following discussions with the Agency regarding the proposed process for review of the interim data from a cardiovascular outcomes trial EFC11319 (ELIXA), that was ongoing at that time. The Clinical Pharmacology review of the Dec 2012 submission was already completed and posted in DARRTS. Lixisenatide NDA was re-submitted on 27 July, 2015. The Clinical Pharmacology review has been updated with additional information that the sponsor submitted. If approved, Lixisenatide will be the 5th approved drug in its class.

Lixisenatide is intended to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted on 07/27/2015 under NDA 208471 and recommend approval with the following recommendations.

- OCP agrees with the sponsor proposed lixisenatide dosing regimen of 10 µg QD as the starting dose for 14 days followed by a maintenance dose of 20 µg from Day 15, to be administered within one hour prior to (b) (4) the first meal of the day (b) (4)
- OCP recommends no dose adjustment for lixisenatide in patients with mild and moderate renal impairment; however, use with caution is recommended. OCP recommends that dose of lixisenatide should be restricted to 10 µg QD in patients with severe renal impairment and should be increased to 20 µg QD only in patients tolerating lixisenatide who require additional glycemic control.
- OCP agrees with the sponsor proposed dosing recommendations for concomitant administration with warfarin, digoxin, and ramipril requiring no dose adjustment.
- In addition, OCP recommends that
 - oral medications that are dependent on threshold concentrations for efficacy, such as antibiotics, should be taken at least 1 hour before lixisenatide injection or with a meal or snack when lixisenatide is not administered
 - patients taking oral contraceptives should be advised to take them at least 1 hour before lixisenatide administration or 11 hours after the morning dose of lixisenatide
 - patients taking atorvastatin should be advised to take atorvastatin preferably 1 hour before lixisenatide administration

A Required OCP Office Level briefing was held on August 12, 2013 (under NDA 204961) to discuss the review team's recommendations. Attendees included Drs. Chandahas Sahajwalla, Issam Zineh, Shiew-Mei Huang, Darrell Abernethy, Mehul Mehta, Vikram Sinha, Suresh Doddapaneni, Brian Booth, Kellie Reynolds, and Anshu Marathe from OCP and Dr. Suchitra Balakrishnan from Office of New Drugs.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

The lixisenatide formulation is a clear, colorless solution (0.05 and 0.1 mg/mL lixisenatide solution) for subcutaneous injection, which is packaged in 3 mL cartridges fitted with (b) (4) closures. Each cartridge contains 0.15 or 0.3 mg of lixisenatide (calculated with reference to the active moiety).

The proposed dosing regimen is that lixisenatide is administered once daily within one hour prior to (b) (4) the first meal of the day (b) (4) and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. For all patients lixisenatide should be initiated with a starting dose of 10 µg for 14 days, followed by a maintenance dose of 20 µg from Day 15.

Key pharmacokinetic properties of lixisenatide are summarized in [Table 1](#). Lixisenatide was interchangeably called as AVE0010 by the sponsor. Throughout this document, any reference to AVE0010 indicates that the drug being discussed is Lixisenatide.

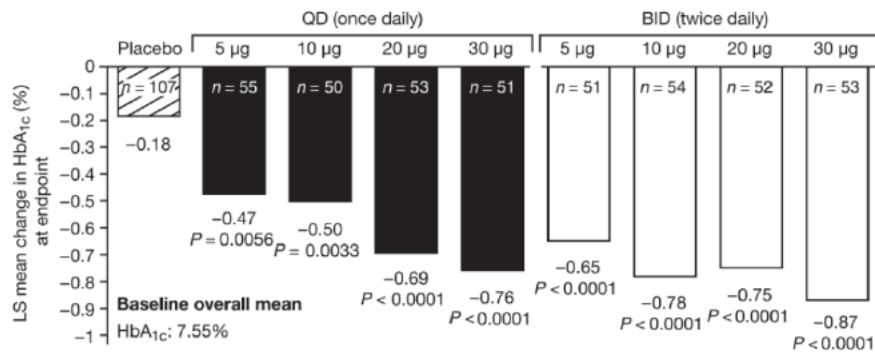
Table 1 Highlights of Pharmacokinetics

Proposed dose	- Starting dose of 10 µg for 14 days; - Maintenance dose of 20 µg from Day 15
Absorption	- Median T_{max} – 1-3.5 h in patients with type 2 diabetes - Dose-proportional PK in the 10 µg-20 µg dose range - Absolute bioavailability reported to be about 32% - Unchanged lixisenatide is the main drug-related component in plasma
Distribution	- Approximately 55% bound to human plasma protein - Mean Vz/F: Approximately 100L following subcutaneous administration, indicating extensive tissue distribution
Metabolism and Elimination	- Lixisenatide, being a peptide, is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation, resulting in smaller peptides and amino acids, which are reintroduced in the protein metabolism. - Apparent terminal half-life: Approximately 3 hours after multiple-dose administration - Apparent clearance (CL/F) is about 35 L/h

1.3.1 Dose/exposure-response relationship for efficacy

HbA_{1c}:

The sponsor studied only one dose of 20 µg QD in all the Phase 3 trials. Majority of the trough concentrations data in the Phase 3 trials were below the limit of quantification. Thus, dose/exposure response relationship for safety and efficacy is limited to data available from a single Phase 2 trial of 13-week duration (Study #DRI6012). In the Phase 2 study, a clear dose response relationship was observed, where increasing doses within the QD and BID-dosing regimen resulted in increase in response in terms of reduction in HbA_{1c} ([Figure 1](#)), secondary efficacy parameter such as fasting plasma glucose and post prandial glucose, and weight loss also showed dose-response relationship. Compared to proposed 20 µg QD dosing, 10 µg BID-dosing regimen showed slight numerically greater reduction in HbA_{1c} (-0.69 with 20 µg QD vs. -0.78 with 10 µg BID-dosing). [Figure 2](#) shows cumulative distribution function (CDF) plots for change from baseline HbA_{1c} between these two dosing regimens. Although a slight difference in mean change from baseline in HbA_{1c} is seen in these two dosing group, overlapping CDF plots between 20 µg QD and 10 µg BID dosing indicates that the distribution for change from base line in HbA_{1c} is similar across both the dosing groups.



BID = twice daily; HbA_{1c} = glycosylated hemoglobin; ITT = intent-to-treat; LS = least square; n = number of patients; QD = once daily

Figure 1 Mean change in HbA_{1c} at endpoint (ITT population)

[Source: Sponsor's Summary of Clinical Efficacy, Figure 10, Page 131]

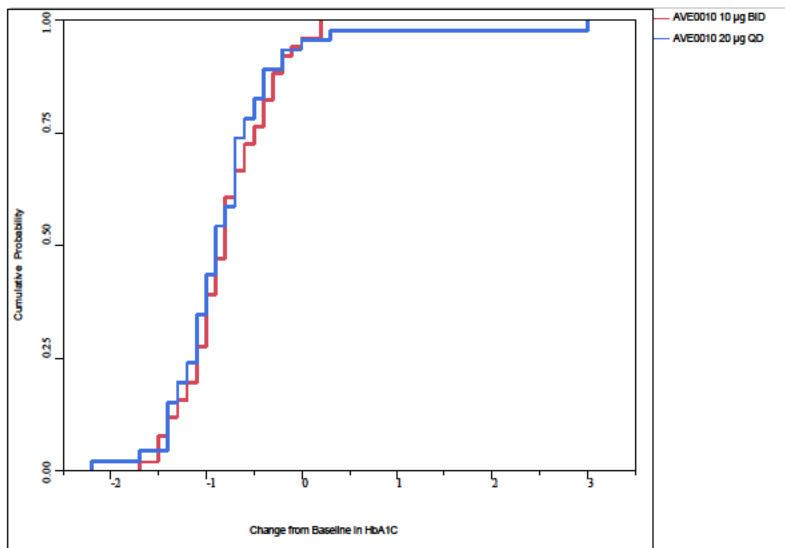


Figure 2 Cumulative distribution function plot for mean change from baseline in HbA_{1c} at week 13 (Study DRI6012).

(AVE0010 10 µg BID = Lixisenatide 10 µg BID dosing; AVE0010 20 µg QD = Lixisenatide 20 µg QD dosing)

Body Weight:

A clear dose-response relationship for weight loss was observed for each dosing regimen, i.e., the higher the lixisenatide dose within a regimen (QD or BID) the larger the mean decrease in body weight. The data for mean change in weight (kg) from baseline to endpoint (week 13) is presented in [Table 2](#). Compared to 10 µg BID dose, 20 µg QD dose had a numerically greater weight loss change.

Table 2 Mean change in weight (kg) from baseline to endpoint – ITT population in Phase 2 Trial (Study#DRI6012)

	QD Dosing					BID Dosing			
	Placebo (n=108)	5 µg (n=55)	10 µg (n=51)	20 µg (n=53)	30 µg (n=52)	5 µg (n=51)	10 µg (n=54)	20 µg (n=52)	30 µg (n=53)
Baseline Mean (SD) Weight (kg)	87.66 (13.69)	84.83 (15.56)	90.66 (17.37)	88.93 (17.11)	87.17 (15.19)	86.26 (14.41)	90.02 (16.90)	88.18 (16.76)	87.55 (13.74)
Change from Baseline Mean (SD) Weight (kg)	-1.51 (2.22)	-1.51 (2.65)	-2.02 (2.64)	-2.59 (3.14)	-3.02 (2.86)	-1.65 (2.56)	-1.85 (2.74)	-2.18 (2.15)	-3.43 (2.68)

1.3.2 Dose/exposure-response relationship for Safety:

The major safety issues associated with lixisenatide were gastrointestinal disorders such as nausea and vomiting. Majority of the trough concentrations data in the Phase 3 trials were below the limit of quantification. In addition, sponsor studied only one dose in all the Phase 3 trials. Thus, dose/exposure response relationship for safety is limited to data available from a single Phase 2 trial of 13-week duration (Study #DRI6012). In the Phase 2 study, a clear dose-response relationship with both regimens was seen in the number of subjects with GI related adverse events. The frequencies for GI side effects ranged from 21.8 % (5 µg) to 51.9 % (30 µg) in lixisenatide QD groups and from 22.6% (5 µg) to 57.4 % (30 µg) in lixisenatide BID groups. Doses higher than 20 µg in both QD and BID dosing regimen resulted in more gastrointestinal related adverse events ([Table 3](#)).

Additionally, compared to 20 µg QD dosing regimen 10 µg BID dosing regimen had less gastrointestinal related side effects.

Table 3 Dose-response relationship for GI disorders in Phase 2 Trial (Study#DRI6012)

	QD Dosing					BID Dosing			
	Placebo (109)	5 µg (55)	10 µg (52)	20 µg (55)	30 µg (54)	5 µg (53)	10 µg (56)	20 µg (54)	30 µg (54)
Subjects with any TEAEs (% of Subjects)	65 (29%)	31 (56.4%)	26 (50%)	37 (67.3%)	42 (77.8%)	30 (56.6%)	32 (57.1%)	38 (70.4%)	40 (74.1%)
Gastrointestinal Disorders (% of Subjects)	21 (19%)	12 (21.8%)	11 (21.2%)	23 (41.8%)	28 (51.9%)	12 (22.6%)	15 (26.8%)	25 (46.3%)	31 (57.4%)

1.3.3 Benefit Risk Comparison of 20 µg QD and 10 µg BID dosing:

Since results of the dose ranging study indicated that 10 µg BID dosing is better than 20 µg QD dosing in terms of efficacy and GI safety, we examined the benefit risk comparison of these two dosing regimen and agree with the sponsor’s proposed dose of 20 µg QD for the following reasons:

Efficacy

- Compared to proposed 20 µg QD dosing, 10 µg BID-dosing regimen showed numerically slight higher reduction in HbA_{1c}. However, the added benefit with 10 µg BID-dosing should be weighed against the narrow time window left for the administration of concomitant medication because of the effect of lixisenatide on delaying gastric emptying time.

- Furthermore, [Figure 2](#) shows that the cumulative distribution plots for change from baseline in HbA_{1c} is highly overlapped between the these two dosing regimens indicating a similar overall distribution of change from baseline in HbA_{1c} in the two dosing groups.
- Compared to 10 µg BID dose, 20 µg QD dose showed a numerically greater reduction in weight.

Safety

- In the dose ranging Phase 2 study, doses higher than 20 µg in both QD and BID dosing regimen resulted in more gastrointestinal related adverse events ([Table 3](#)).
- Additionally, compared to 20 µg QD dosing regimen, 10 µg BID dosing regimen had less gastrointestinal related side effects. However, as stated above the added safety benefit with BID dosing regimen needs to be counterbalanced with the inconvenience of co-administration of other drugs.

Practicality

- Lixisenatide delays the gastric emptying time and hence concomitant medications need to be administered ^{(b) (4)} 1 hour before lixisenatide administration or with next meal for those drugs that have to be administered with food.
- With BID dosing regimen, the subjects will have a narrow window for taking concomitant medications and hence we agree with the sponsor's proposed 20 µg QD dosing regimen as acceptable from a practical standpoint.

1.3.4 Intrinsic Factors

- Age: No clinically relevant effect on the pharmacokinetics of lixisenatide
- Gender: No clinically relevant effect on the pharmacokinetics of lixisenatide
- Race: No clinically relevant effect on the pharmacokinetics of lixisenatide
- Body weight: No clinically relevant effect on lixisenatide AUC
- Renal and Hepatic impairment: see below

1.3.5 Drug-Drug Interactions:

- **Acetaminophen:** This drug interaction study was conducted to evaluate lixisenatide's effect on delaying GI motility. When administered 1 or 4 hours after 10 µg lixisenatide, on average, AUC of acetaminophen was unaltered, C_{max} of acetaminophen was decreased by 29% and 31% respectively, and median t_{max} was delayed by 2.0 and 1.75 hours respectively. No dose adjustment for acetaminophen is recommended. This study clearly demonstrated that a 10 µg dose of lixisenatide can have a delaying effect of up to 4 hours on absorption of drugs such as acetaminophen which are absorbed rapidly with a short t_{max} (1-3 hours). Sponsor did not conduct a study with the 20 µg dose of lixisenatide. Oral medications that are dependent on threshold concentrations for efficacy, such as antibiotics, should be taken at least 1 hour before lixisenatide injection or with a meal or snack when lixisenatide is not administered.
- **Oral contraceptives:** Administration of an oral contraceptive 1 hour or 4 hours after lixisenatide did not affect AUC and t_{1/2} of ethinylestradiol and levonorgestrel, whereas C_{max} of ethinylestradiol was decreased by 52% and 39% respectively and C_{max} of levonorgestrel was decreased by 46% and 20%, respectively and median t_{max} was delayed by 1 to 3 hours. There was no change in AUC. The clinical implications of reduced peak exposure of ethinylestradiol and levonorgestrel when the oral contraceptive was administered 1 hour or 4 hours after lixisenatide injection, is unknown. It is quite possible that oral contraceptives depend on threshold concentrations for efficacy. Therefore, patients should be advised to

take oral contraceptives at least 1 hour before lixisenatide administration or 11 hours after the morning dose of lixisenatide.

- **Atorvastatin:** The steady-state C_{max} of atorvastatin was reduced by 31%, AUC was unaltered, and t_{max} was prolonged (with change in t_{max} ranging from -1 to 9 hours) when atorvastatin was administered in morning 1 hour after lixisenatide injection. However, when atorvastatin was administered in evening 12.5 hours following lixisenatide administration in the morning, C_{max} of atorvastatin was increased by 66%, AUC was increased by 27%, and t_{max} was unaltered (with change in t_{max} ranging from -3 to 2 hours). The 31% decrease in C_{max} observed for the morning dosing is not clinically relevant based on atorvastatin prescribing information; however, the significance of the effect of prolongation in t_{max} by up to 9 hours is not known. Although an increase in C_{max} and AUC was seen for evening administration, the increase in these parameters was only 25% and 18%, respectively, when comparing the atorvastatin evening administration following lixisenatide morning administration vs. atorvastatin administered alone in the morning. Since the safety and efficacy for atorvastatin administered alone in the morning is established, the 18-25% increase in exposure may not be clinically relevant. Further there were safety data available from completed Phase 3 trials for co-administration with statins. It showed that trends of treatment-emergent adverse events in the lixisenatide and placebo groups were not affected by concomitant statin use (85.3% in the lixisenatide group and 79.0% in the placebo group with statin use compared with 76.7% in the lixisenatide group and 65.2% in the placebo group without statin use). Based on safety information from Phase 3 trials, and information garnered from approved label for atorvastatin that LDL-C reduction is the same regardless of the time of day of drug administration, no dose adjustment is recommended for atorvastatin. However, because it may take longer to reach steady-state concentrations of atorvastatin when administered with lixisenatide, patients taking atorvastatin may be advised to take atorvastatin preferably 1 hour before lixisenatide administration.
- **Warfarin and other coumarin derivatives:** In this DDI study, warfarin was administered either in the morning on Day 1 of the treatment period without concomitant lixisenatide treatment (Treatment A), or on Day 11 of the treatment period with concomitant lixisenatide treatment (Treatment B). Lixisenatide was administered 30 minutes before breakfast while the single oral dose of 25 mg warfarin was administered with breakfast. While AUC did not change between warfarin alone and warfarin+lixisenatide treatments (ratio 1.03), C_{max} reduced 19% and 15% for S-warfarin and R-warfarin, respectively, when warfarin was administered after lixisenatide. There was, however, a shift in T_{max} from 1 hour post warfarin alone treatment to 8.0 hours post warfarin+lixisenatide treatment. The implication of the 7-hour delay in time to peak warfarin concentration is unknown. While no dose adjustment for warfarin is required when co-administered with lixisenatide based on lack of pharmacokinetic interaction, frequent monitoring of INR in patients on warfarin and/or coumarin derivatives, as well as following of instructions in the warfarin product monograph for appropriate monitoring and dose adjustment is recommended at the time of initiation or ending of lixisenatide treatment.
- **Digoxin:** When digoxin was administered 30 minutes post lixisenatide injection, the steady-state C_{max} of digoxin was reduced by 26% compared to digoxin alone. Steady-state AUC for digoxin remained unchanged between the treatments. T_{max} was prolonged from 0.5 hours with digoxin alone to 2 hours following digoxin given 30 minutes post lixisenatide injection. Due to the lixisenatide induced delay in time to peak digoxin concentrations, careful monitoring of digoxin levels are recommended. The health care provider should be cautioned to follow instructions in the product monograph for digoxin for appropriate dose adjustment, if necessary when administering with lixisenatide.

- Ramipril:** When ramipril was administered 30 minutes post lixisenatide injection, the steady-state C_{max} of ramipril was reduced by 73% compared to ramipril alone. Steady-state AUC for ramipril was increased by 21%. T_{max} was prolonged from 0.5 hours with ramipril alone to 2.8 hours following ramipril given 30 minutes post lixisenatide injection. For ramiprilat, the active moiety of ramipril, however, there was essentially no change in C_{max} (ratio 1.02) and AUC (ratio 1.11) between ramipril+lixisenatide and ramipril treatments. T_{max} for ramiprilat was prolonged from 2.5 hours with ramipril alone to 5.0 hours following ramipril given 30 minutes post lixisenatide injection. Mean trough concentrations of ramiprilat were similar between the two treatments (1.85 ng/mL following ramipril alone vs. 1.94 ng/mL following ramipril+lixisenatide). Ramipril is almost completely metabolized in the body to Ramiprilat, which has about 6 times the ACE inhibitory activity of Ramipril. Since the total exposure and trough concentrations of ramiprilat did not change following administration with lixisenatide compared to lixisenatide alone, no dose adjustment for ramipril is suggested when co administered with lixisenatide.

1.3.5.1 Specific Population

1.3.5.1.1 Hepatic Impairment

No dosing adjustment is recommended in patients with hepatic impairment. This is similar to the dosing recommendation for other biologics.

1.3.5.1.2 Renal Impairment

No dose adjustment is recommended in patients with mild renal impairment, however, use with caution is recommended because of the higher incidences of nausea, vomiting and percentage of hypoglycemic events observed in this population compared to normal subjects in the Phase 3 studies.

There were no unique safety concerns observed in patients with moderate renal impairment. The sample size was small in the Phase 3 trials to draw any conclusions. However, 215 patients with moderate renal impaired were enrolled on lixisenatide in the dedicated CV safety trial (ELIXA trial), safety assessment of which did not show any unique safety concerns. Therefore, no dosing adjustment is recommended in patients with moderate renal impairment; however, use with caution is recommended because of general concerns of dehydration leading to acute renal failures with this class of drugs. Please refer to the clinical review by Dr. Suchitra Balakrishnan for complete details of the results for patients with moderate renal impairment from efficacy and safety trials.

There were only 3 patients with severe renal impairment in the ELIXA trial. The sponsor proposed not to use lixisenatide in patients with severe renal impairment. However, given that efficacy of lixisenatide is preserved in patients with renal impairment and that there is no unique safety concerns in this population, this reviewer recommends that lixisenatide should be used with caution in patients with severe renal impairment. The dose of lixisenatide should be restricted to 10 μ g QD in patients with severe renal impairment, and should be increased to 20 μ g QD only in patients tolerating lixisenatide who require additional glycemic control.

The recommendation for 10 μ g QD dose in patients with severe RI is based on exposure matching.

2 Question-Based Review (QBR)

Lixisenatide NDA was originally submitted on 12/20/2012 under NDA 208471, and subsequently withdrawn in October 2013. The Clinical Pharmacology was completed and posted in DARRTS prior to the sponsor's withdrawal of the NDA. The NDA was re-submitted on 07/27/2015, under NDA 208471. Information from 4 new studies are available in this re-submission. Clinical Pharmacology findings from these studies are discussed in a separate addendum in Section 2.8.

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and Clinical studies with PK and/or PD information submitted in the NDA

The clinical pharmacology program performed to evaluate the pharmacokinetic and pharmacodynamic properties of lixisenatide included 26 clinical pharmacology trials. These comprised 17 Phase 1 trials in healthy subjects (including bioequivalence trials, trials in elderly subjects, subjects with renal impairment and Chinese subjects) and 5 trials (2 Phase 1 and 3 Phase 2) in subjects with type 2 diabetes (including one trial in Japanese subjects), and 3 Phase 3 studies from which PK data were available. The program was supported by 8 human biomaterial studies, which have been conducted to provide supporting information on the clinical pharmacology of lixisenatide ([Table 4](#)).

These *in vitro* studies investigated protein binding, metabolic stability of lixisenatide in S9 liver and kidney fractions and identification of metabolites, the potential for lixisenatide to induce cytochrome P450 (CYP) isozyme activity in human hepatocytes or inhibit CYP isozyme activity in human liver microsomes, and the potential for lixisenatide to inhibit human organic cation transporter 2 (OCT2) (kidney) and organic anion transporting polypeptide 1B1 (OATP1B1) (liver) uptake transporters. A list of all completed clinical pharmacology studies is provided in [Table 5](#).

Table 4 Overview of human biomaterial studies with lixisenatide

Study type	Document number	Biomaterial	Lixisenatide concentration ^a	Report location
Distribution				
Protein binding	LPR0930	Human plasma	500 to 50 000 pg/mL (0.103 to 10.3 nM)	[5.3.2.1]
Metabolism				
In vitro metabolism	00-039	Human and animal plasma	1002 nM (4 860 000 pg/mL)	[4.2.2.4]
In vitro metabolism	F2006KIN0001	Human and animal S9 liver and kidney fractions	5000 nM (24 300 000 pg/mL)	[4.2.2.4]
In vitro metabolism	F2005KIN0246	Human S9 kidney fraction	50 to 5000 nM (243 000 to 24 300 000 pg/mL)	[5.3.2.3]
CYP induction potential	MIH0797	Human hepatocytes	0.037 to 37 nM (180 to 180 000 pg/mL)	[5.3.2.2]
CYP inhibition potential	MIH0332	Human liver microsomes	50 to 20 000 nM (243 000 to 98 000 000 pg/mL)	[5.3.2.2]
CYP2C8 inhibition potential	MIH0544	Human liver microsomes	3 to 200 000 nM (14 580 to 980 000 000 pg/mL)	[5.3.2.2]
Elimination				
Inhibition potential for human OCT2 (kidney) and OATP1B1 (liver) uptake transporters	TRE0028	Human recombinant cell lines	0.037 to 37 nM (180 to 180 000 pg/mL)	[5.3.2.3]

^a Concentrations in parentheses have been calculated manually to enable comparison of information across studies
CYP = cytochrome P450; OCT2 = organic cation transporter 2; OATP1B1 = organic anion transporting polypeptide 1B1

Table 5: Overview of studies with pharmacokinetic and pharmacodynamic assessments relevant to the clinical pharmacology of lixisenatide

Study type	Study location/ code	Lixisenatide dosing	Number of subjects treated with lixisenatide	Available data		
				PK ^a	PD ^b (lixisenatide)	PK/PD
Pharmacokinetics in healthy subjects (Phase 1 studies) – summarized in [2.7.1]						
Bioequivalence of 2 formulations	5.3.1.2 [BEQ11094]	Single, 10 µg	90	Lixisenatide	–	–
Relative bioavailability at 3 application sites	5.3.1.2 [BDR6864]	Single, 10 µg	43	Lixisenatide	–	–
Effect of intrinsic factors on pharmacokinetics in healthy subjects (Phase 1 studies)						
Effect of age (elderly)	5.3.3.3 [POP11814]	Single, 20 µg	36	Lixisenatide	–	–
Effect of renal impairment	5.3.3.3 [POP6053]	Single, 5 µg	32	Lixisenatide	–	–
Effect of race (Chinese)	5.3.3.3 [POP11320]	Multiple, QD, 7 days at 10 µg + 7 days at 20 µg (14 days total)	22	Lixisenatide	–	–
Effect of lixisenatide on the pharmacokinetics of other drugs in healthy subjects (Phase 1 studies)						
Oral contraceptive (women) interaction	5.3.3.4 [INT6052]	Single ^c , 10 µg (placebo-controlled)	25	Ethinylestradiol, levonorgestrel Lixisenatide (at 2 hours only)	–	–
Acetaminophen interaction	5.3.3.4 [INT6863]	Single, 10 µg (placebo-controlled)	15	Acetaminophen Lixisenatide (at 1, 2, and 4 hours only)	–	–

Study type	Study location/ code	Lixisenatide dosing	Number of subjects treated with lixisenatide	Available data		
				PK ^a	PD ^b (lixisenatide)	PK/PD
Warfarin interaction	5.3.3.4 [INT10408]	Multiple, QD, 7 days at 10 µg + 10 days at 20 µg (17 days total)	16	S-warfarin, R-warfarin Lixisenatide	–	–
Atorvastatin interaction	5.3.3.4 [INT10409]	Multiple, QD, 7 days at 10 µg + 7/8 days at 20 µg (14/15 days total)	34	Atorvastatin, ortho-OH- atorvastatin, para-OH- atorvastatin Lixisenatide	–	–
Ramipril interaction	5.3.3.4 [INT10782]	Multiple, QD, 7 days at 10 µg + 7 days at 20 µg (14 days total)	30	Ramipril, ramiprilat Lixisenatide	–	–
Digoxin interaction	5.3.3.4 [INT10783]	Multiple, QD, 7 days at 10 µg + 10 days at 20 µg (17 days total)	24	Digoxin Lixisenatide	–	–
Pharmacodynamics in healthy subjects (Phase 1 studies)						
Pharmacodynamic response under hypoglycemic conditions	5.3.4.1 [PDY11941]	Single, 20 µg (placebo-controlled)	17	Lixisenatide	Glucagon, counterregulatory hormones, insulin, C-peptide	–
Effect on first-phase insulin response	5.3.4.1 [PDY11824]	Single, 20 µg (placebo-controlled)	20	Lixisenatide	Insulin, C-peptide, glucose, glucagon	–
Gallbladder motility	5.3.4.1 [PDY11431]	Single, 20 µg (placebo-controlled)	24	Lixisenatide	Gallbladder ejection fraction	–

Study type	Study location/ code	Lixisenatide dosing	Number of subjects treated with lixisenatide	Available data		
				PK ^a	PD ^b (lixisenatide)	PK/PD
Electrocardiogram parameters	5.3.4.1 [TES6865]	Multiple, QD, 7 days at 10 µg, 7 days at 15 µg, and 14 days at 20 µg (28 days total) and Multiple, BID, 7 days at 10 µg BID, 7 days at 20 µg BID, 13 days at 30 µg BID, and 1 day at 30 µg QD (28 days total) (placebo-controlled and active controlled [moxifloxacin])	47	Lixisenatide	QTcF and other ECG parameters	QTcF and other ECG parameters
Electrocardiogram parameters	5.3.4.1 [TES11807]	Multiple, QD, 7 days at 10 µg, 7 days at 15 µg, and 14 days at 20 µg (28 days total) and Multiple, BID, 7 days at 10 µg BID, 7 days at 20 µg BID, 13 days at 30 µg BID, and 1 day at 30 µg QD (28 days total) (placebo-controlled and active controlled [moxifloxacin])	133	Lixisenatide	QTcF and other ECG parameters	QTcF and other ECG parameters
Spermatogenesis	5.3.4.1 [TDR11215]	Multiple, QD, 3 days at 10 µg, 4 days at 15 µg, and 175 days at 20 µg (182 days total) (placebo-controlled)	138	Lixisenatide	Sperm production parameters	–

Study type	Study location/ code	Lixisenatide dosing	Number of subjects treated with lixisenatide	Available data		
				PK ^a	PD ^b (lixisenatide)	PK/PD
Pharmacodynamics in patients with T2DM (Phase 1 studies)						
Dose escalation, initial safety and tolerability	5.3.3.2 [01-016]	Single, 1 to 40 µg (placebo-controlled)	18	-	Blood glucose, insulin, C-peptide, glucagon	-
Effect on first-phase insulin response	5.3.4.2 [PDY10433]	Single, 20 µg (placebo-controlled)	21	Lixisenatide	Insulin, C-peptide, glucagon	-
Pharmacodynamics in patients with T2DM (Phase 2 studies)						
Dose escalation	5.3.4.2 [ACT6011]	Multiple, QD or BID, up to 20 µg for 28 days Starting dose: 5 µg, increased in increments of 2.5 µg at 4-day intervals up to 28 days (placebo-controlled)	42	Lixisenatide	Blood glucose, insulin, C-peptide, glucagon, gastric emptying rate, HbA _{1c} , body weight	AUC of lixisenatide versus change in AUC of blood glucose (in antibody-negative patients)
Dose response	5.3.5.1 [DRI6012]	Multiple, QD or BID 5, 10, 20, or 30 µg for 13 weeks For dose levels 20 and 30 µg: Starting dose: 10 µg, to be increased in weekly increments of 5 µg (placebo-controlled)	433	Lixisenatide	HbA _{1c} , plasma glucose, insulin, C-peptide, glucagon, fructosamine, body weight	Population analysis of AUC of lixisenatide versus AUC of plasma glucose

Study type	Study location/ code	Lixisenatide dosing	Number of subjects treated with lixisenatide	Available data		
				PK ^a	PD ^b (lixisenatide)	PK/PD
Dose escalation in Japanese and Caucasian patients	5.3.5.1 [PDY6797]	Single, 5 or 10 µg and Multiple, QD or BID, up to 30 µg for 6 weeks Starting dose: 5 or 10 µg, to be increased in weekly increments of 5 µg (placebo-controlled)	80	Lixisenatide (plasma and urine)	Plasma glucose, insulin, glucagon, fructosamine, HbA _{1c} , body weight	Population analysis of AUC of lixisenatide versus AUC of plasma glucose
Postprandial glucose versus liraglutide	5.3.4.2 [PDY10931]	Multiple, QD, 14 days at 10 µg and 14 days at 20 µg (28 days total) (active controlled, liraglutide)	77	-	Plasma glucose, insulin, C-peptide, glucagon, HbA _{1c} , satiety markers	-
Pharmacokinetic data from patients with T2DM (Phase 3 studies) – summarized in [2.7.3]						
Effect on glycemic control (HbA _{1c})	5.3.5.1 [EFC6015]	Multiple, QD, 1 week at 10 µg, 1 week at 15 µg, and 22 weeks at 20 µg (24 weeks total double-blind period), followed by variable extension period up to Week 76 (placebo-controlled)	574	Lixisenatide (population analysis)	-	-

Study type	Study location/ code	Lixisenatide dosing	Number of subjects treated with lixisenatide	Available data		
				PK ^a	PD ^b (lixisenatide)	PK/PD
Effect on glycemic control (HbA _{1c})	5.3.5.1 [EFC6018]	Multiple, QD, 1 week at 10 µg, 1 week at 15 µg, and 10 weeks at 20 µg (12 weeks total)	120	Lixisenatide (population analysis)	–	–
		or Multiple, QD, 2 weeks at 10 µg and 10 weeks at 20 µg (12 weeks total) (placebo-controlled)	119			
Effect on glycemic control (HbA _{1c})	5.3.5.1 [EFC10887]	Multiple, QD, 1 week at 10 µg, 1 week at 15 µg, and 22 weeks at 20 µg (24 weeks total) (placebo-controlled)	154	Lixisenatide (population analysis)	–	–

^a Plasma PK (unless indicated otherwise)

^b As relevant to this document (2.7.2 Summary of Clinical Pharmacology Studies)

^c 1 dose per treatment period

AUC = area under the concentration versus time curve; BID = twice daily; ECG = electrocardiogram; HbA_{1c} = glycosylated hemoglobin; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QD = once daily; QT = ventricular depolarization and repolarization time on electrocardiogram; QTcF = QT interval corrected according to Fridericia's formula; T2DM = type 2 diabetes mellitus

The clinical program performed to evaluate the efficacy and safety of lixisenatide included 14 Phase 3 trials of which 12 studies have been completed as of the NDA cut-off date of 01 June 2012 and 2 studies are ongoing. Change in HbA_{1c} was the primary endpoint in 9 double-blind placebo-controlled studies. In an active-controlled study conducted to support the claim of efficacy, the primary endpoint was a composite endpoint of reduction in both HbA_{1c} and body weight. This study was conducted in obese, T2DM, younger than 50 population. A listing of Phase 3 studies with lixisenatide is presented in [Table 6](#).

Table 6 Clinical Phase 3 studies in patients with T2DM: Completed studies as of 01 June 2012

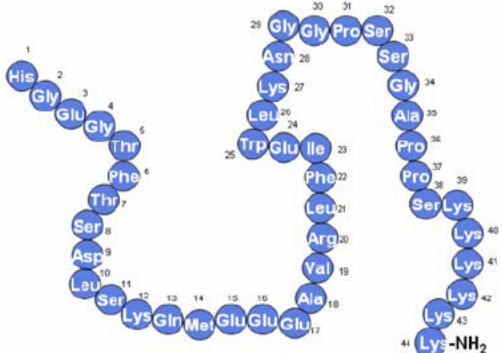
Study (background treatment)	Primary objective	Lixisenatide dose (number of randomized patients)	Lixisenatide dose, form, regimen	Control (number of randomized patients)	Design	Treatment period
<i>Pivotal studies</i>						
EFC6014/GetGoal-M (metformin) (see 5.3.5.1 [EFC6014])	Efficacy of lixisenatide on glycemic control (HbA _{1c}) when it is used in the morning within 1 hour prior to a meal over 24 weeks	20 µg QD (total= 510) Morning (n=255) Evening (n=255)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Placebo (total=170) Morning (n=85) Evening (n=85)	Multinational, randomized, double-blind, 4-arm, unbalanced design, parallel-group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC6015/GetGoal-S (SU ± metformin) (see 5.3.5.1 [EFC6015])	Effects of lixisenatide on glycemic control (HbA _{1c}) over 24 weeks	20 µg QD (n=573)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg)	Placebo (n=286)	Multinational, randomized, double-blind, 2-arm, unbalanced design, parallel-group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC6016/GetGoal-L (basal insulin ± metformin) (see 5.3.5.1 [EFC6016])	Efficacy of lixisenatide on glycemic control (HbA _{1c}) over 24 weeks	20 µg QD (n=329)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Placebo (n=167)	Multinational, randomized, double-blind, 2-arm, unbalanced design, parallel-group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC6017/GetGoal-P (TZD ± metformin) (see 5.3.5.1 [EFC6017])	Efficacy of lixisenatide on glycemic control (HbA _{1c}) over 24 weeks	20 µg QD (n=323)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Placebo (n=161)	Multinational, randomized, double-blind, 2-arm, unbalanced design, parallel-group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC6018/GetGoal-Mono (none) (see 5.3.5.1 [EFC6018])	Effects of lixisenatide on glycemic control (HbA _{1c}) over 12 weeks, using a 2-step dose increase regimen	20 µg QD (total=239) 2-step (n=120) 1-step (n=119)	- 2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) - 1-step (10 µg for 2 weeks, then maintenance dose of 20 µg QD)	Placebo (total=122) 2-step (n=61) 1-step (n=61)	Multinational, randomized, double-blind, 4-arm, unbalanced design, parallel-group	12 weeks
EFC6019/GetGoal-X (metformin) (see 5.3.5.1 [EFC6019])	Efficacy of lixisenatide on glycemic control (HbA _{1c}) when it is used in the morning within 1 hour prior to a meal over 24 weeks	20 µg QD (n=318*)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Exenatide: 1-step dose increase (5 µg BID for 4 weeks, and maintenance dose of 10 µg BID) (n=316*)	Multinational, randomized, open-label, 2-arm, parallel-group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC10743/GetGoal-F1 (metformin) (see 5.3.5.1 [EFC10743])	Effects of lixisenatide on glycemic control (HbA _{1c}) over 24 weeks, using a 2-step dose increase regimen	20 µg QD (total=322) 2-step (n=161) 1-step (n=161)	- 2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) - 1-step (10 µg for 2 weeks, then maintenance dose of 20 µg QD)	Placebo (total=162) 2-step (n=80) 1-step (n=82)	Multinational, randomized, double-blind, 4-arm, unbalanced design, parallel-group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC10781/GetGoal-Duo1 (insulin glargine + metformin ± TZD) (see 5.3.5.1 [EFC10781])	Effects of lixisenatide on glycemic control (HbA _{1c}) over 24 weeks	20 µg QD (n=223)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Placebo (n=223)	Multinational, randomized, double-blind, 2-arm, parallel-group	24 weeks
EFC10887/GetGoal-L-Asia (basal insulin ± SU) (see 5.3.5.1 [EFC10887])	Effects of lixisenatide on glycemic control (HbA _{1c}) over 24 weeks	20 µg QD (n=154)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Placebo (n=157)	Multinational (Asia), randomized, double-blind, 2-arm, parallel-group	24 weeks
EFC11321/GetGoal-M-Asia (metformin ± SU) (see 5.3.5.1 [EFC11321])	Effects of lixisenatide on glycemic control (HbA _{1c}) over 24 weeks	20 µg QD (n=196)	1-step (10 µg QD for 2 weeks, then maintenance dose of 20 µg QD)	Placebo (n=195)	Multinational (Asia), randomized, double-blind, 2-arm, parallel-group	24 weeks
<i>Supportive study</i>						
EFC10780 (metformin) (see 5.3.5.1 [EFC10780])	Efficacy of lixisenatide on a composite endpoint of HbA _{1c} and body weight over 24 weeks in obese patients younger than 50	20 µg QD (n=158)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Sitagliptin 100 mg QD orally (n=161)	Multinational, randomized, double-blind, double-dummy, 2-arm, parallel-group	24 weeks
<i>Uncontrolled study</i>						
LTS10888/GetGoal-Mono Japan LTS (none) (see 5.3.5.2 [LTS10888])	Safety of lixisenatide QD treatment in monotherapy at Week 24 comparing 1-step and 2-step dose increase regimens in Japan (efficacy was a secondary objective)	20 µg QD (total=69) 2-step (n=33) 1-step (n=36)	- 2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) - 1-step (10 µg for 2 weeks, then maintenance dose of 20 µg QD)	None	Multicenter (Japan), randomized, uncontrolled, open-label, 2-arm, parallel-group	76 weeks (52-week main treatment period; then 24-week extension)

*In Study EFC6019, 639 patients (320 in the lixisenatide group and 319 in the exenatide group) were randomized and treated, but 5 patients from 1 site were excluded from all analyses because of a significant noncompliance with the protocol.
SU: sulfonylurea; TZD: thiazolidinedione; BID: twice daily; QD: once daily

2.2 General Attributes

Lixisenatide is a human Glucagon-Like Peptide-1 (GLP-1) analog and acts as a GLP-1 receptor agonist. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells.

2.2.1 What are the highlights of the Lixisenatide drug product as they relate to clinical pharmacology review?

Lixisenatide	
Appearance	(b) (4) white to off-white powder
Chemical Name (IUPAC)	H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-NH ₂
Molecular Formula	C ₂₁₅ H ₃₄₇ N ₆₁ O ₆₅ S
Molecular Weight	4858.5
Structural Formula	
Solubility	(b) (4)
Melting Point	
UV spectrum	

2.2.2 What is the composition of to-be-marketed formulation of Lixisenatide?

Formulation: Lixisenatide is a clear, colorless solution (0.05 and 0.1 mg/mL lixisenatide solution) for subcutaneous injection, which is packaged in 3 mL cartridges fitted with (b) (4) closures. Each cartridge contains 0.15 or 0.3 mg of lixisenatide (calculated with reference to the active moiety). The pH of the solution is about (b) (4). The solution contains the following excipients: water for injection, glycerol (85 per cent), sodium acetate trihydrate, methionine, metacresol, and hydrochloric acid/sodium hydroxide solution for pH adjustment. A prefilled green pen delivering 14 doses of 10 µg and a prefilled (b) (4) pen delivering 14 doses of 20 µg are available. Each green pre filled pen contains 3 mL solution and each mL contains 50 µg (0.05 mg/mL) lixisenatide. Each (b) (4) pre filled pen contains 3 mL solution, and each mL contains 100 µg (0.1 mg/mL) lixisenatide. The formulation is shown in [Table 7](#).

Table 7 Phase 3/commercial formulation

Components ^a	Composition						Function	Reference to standards ^b	
	Percentage [%]		per mL [mg]		Per unit (3 mL cartridge) [mg]				
Dosage strengths [mg/mL]	0.05	0.1	0.05	0.1	0.05	0.1			
Lixisenatide	0.005	0.01	0.05	0.1	0.15	0.3	Active substance (b) (4)	In-house	
Glycerol (85 per cent)	1.8		18.0		54.0			Ph. Eur.	
Sodium acetate trihydrate [Sodium acetate]	0.35		3.5		10.5			Ph. Eur., USP	
Methionine	0.3		3.0		9.0			Ph. Eur., USP	
Metacresol ^c	0.27		2.7		8.1			Ph. Eur., USP	
Hydrochloric acid, (b) (4) [Hydrochloric acid]	---		q.s. pH (b) (4)		q.s. pH (b) (4)			Ph. Eur., NF	
Sodium hydroxide	---		q.s. pH (b) (4)		q.s. pH (b) (4)			Ph. Eur., NF	
Water for injection								(b) (4)	Ph. Eur., USP
								(b) (4)	Ph. Eur., NF

^a Components are listed according to their pharmacopoeial names. If more than one monograph exists, other names are given in brackets, along with the compendial origin.

^b Reference is made to the current edition of the Pharmacopoeia.

^c For metacresol, the common chemical name "m-cresol" is also used within the dossier.

(Source: Lixisenatide NDA eCTD module 2.3.P; Table 1, page 7)

2.2.3 What are the proposed mechanism of action and therapeutic indications?

Glucagon-like peptide 1 is secreted from the L-cells of the lower gastrointestinal tract (mainly, from the ileum and colon) following the ingestion of a carbohydrate- or fat-containing meal. GLP-1 is known to regulate nutrient metabolism via stimulating effects on insulin release from the pancreatic islets (insulinotropic release), which also affects glucagon secretion (suppressive effect), gastric motility (slowing of gastric emptying), and stomach acid secretion.

All these pharmacodynamic (PD) effects have been demonstrated in clinical studies employing exogenous GLP-1. The insulinotropic effect is glucose dependent, at glucose concentrations below approximately 4.5 mM, insulin secretion is not stimulated, thus minimizing the risk of relevant hypoglycemia. The slowing of gastric emptying together with a GLP-1 related increase in satiety (mediated through the central nervous system) may decrease body weight despite the insulinotropic effects.

The active, circulating form of GLP-1 in humans is GLP-1 (7-36)-amide. GLP-1 has a very short half-life in circulation (<2 minutes) mainly because of rapid N-terminal cleavage by the common, dipeptidyl peptidase-4 (DPP-4). Lixisenatide, an analog of exendin, a naturally occurring peptide is resistant to degradation by DPP-4.

In vitro pharmacology studies in Chinese hamster ovary (CHO) cells transfected with the human GLP-1 receptor showed that lixisenatide had a binding affinity ~4 times greater than native human GLP-1. The IC₅₀ of lixisenatide was 1.43 nmol/L vs. a GLP-1 IC₅₀ of 5.48 nmol/L, which corresponds to K_i values of 1.33 and 5.09 nmol/L, respectively.

(b) (4)
Lixisenatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

2.2.4 What are the proposed dosages and routes of administration?

Lixisenatide injection 10 µg and 20 µg to be administered subcutaneously are the proposed commercial strengths. The sponsor's proposed dosing recommendation is to start with a 10 µg once daily dose for 14 days followed by a 20 µg once-daily maintenance dose. Lixisenatide should be administered once daily

within one hour prior to (b) (4) the first meal of the day (b) (4) If a dose is missed, lixisenatide should be injected within the hour preceding the next meal.

In addition, the following dosing recommendations are proposed by the sponsor:

(b) (4)

When lixisenatide is added to a sulfonylurea or a basal insulin, there is a potential risk of hypoglycemia (based on results from studies EFC6016, EFC10887). A reduction of the concomitantly administered sulfonylurea or basal insulin may be necessary based on clinical experience.

2.3 General Clinical Pharmacology

2.3.1 *What are the PK characteristics of lixisenatide after subcutaneous administration and how do they relate to the dose?*

2.3.1.1 *Single Dose*

Single-dose pharmacokinetics of lixisenatide in healthy subjects are available from 7 single dose studies across a dose range of 5 µg to 20 µg (studies BDR6864, BEQ11094, PDY11431, PDY11824, PDY11941, POP11814, and POP6053). Single dose data for the plasma PK of lixisenatide in patients with T2DM are available from Study PDY10433 with a 20 µg dose, and from the first dose in Study PDY6797 (5 or 10 µg). Upon SC administration, maximum concentrations of lixisenatide in systemic circulation were achieved between 1.5 - 3 hours in healthy subjects and between 1 – 3.5 hours in T2DM patients.

A population PK analysis by the sponsor indicated that lixisenatide has absorption-limited PK because the calculated population mean absorption time (MAT) of 3.25 hours was longer than the population mean elimination time (V/CL) of 1.06 hours (flip-flop kinetics). In healthy subjects as well as patients with T2DM, the extent of absorption (as reflected by the AUC and C_{max}) appeared to be less than dose proportional after single dose administration of lixisenatide across dose levels of 5 to 20 µg. Further discussion is included in section 2.4.

The reported *in vitro* plasma protein binding of lixisenatide is low (~55%), and is largely independent of concentration. The volume of distribution in healthy subjects generally ranged between 60 and 120 L after single dosing, irrespective of the dose level administered, suggesting that lixisenatide is distributed throughout the body. Similarly, in patients with T2DM, the volume of distribution ranged between approximately 70 and 140 L after single dosing, irrespective of the dose level administered.

Across these dose groups, the elimination half- life was approximately 1.5 hours for healthy subjects as well as T2DM patients.

Representative mean plasma concentration-time profiles of lixisenatide following single-dose are illustrated in [Figure 3](#) below for normal healthy volunteers and T2DM patients.

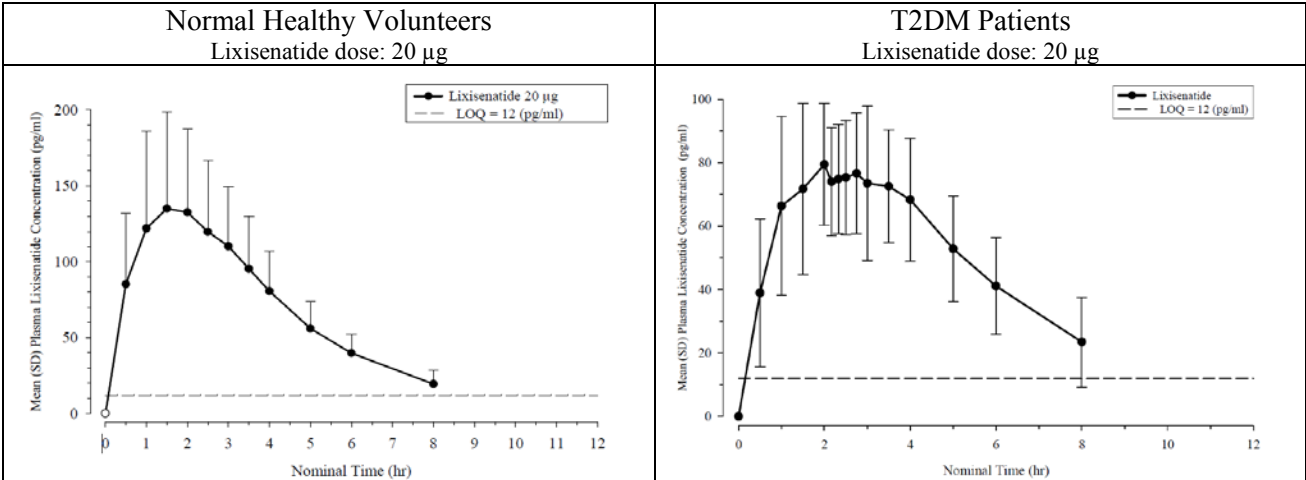


Figure 3 Mean plasma concentration time profile of lixisenatide after a single-dose 20 µg SC dose
(Source: study PDY11824, Figure 6, Page 64; study PDY10433, Figure 6, page 68)

The mean and SD of pharmacokinetic parameters for lixisenatide across the single-dose studies are presented in [Tables 8](#) and [9](#) below.

Table 8 Pharmacokinetic parameters of lixisenatide after single subcutaneous doses from 5 µg to 20 µg in healthy subjects.

Dose (µg)	Study	N ^a	Geometric mean (%CV)					Median (range)		
			AUC (pg.h/mL)	AUC _{last} (pg.h/mL)	C _{max} (pg/mL)	CL/F (L/h)	V _z /F (L)	t _{1/2z} (h)	t _{max} (h)	
5	non-renal impaired	POP6053	8	258 (34)	195 (43)	48 (52)	19 (31)	64 (35)	2.5 (38.0)	2.3 (0.5 : 3.0)
10	Abdomen	BDR6864	42	378 (31)	253 (45)	57 (35)			2.8 (69.3)	2.0 (0.5 : 4.0)
10	Thigh	BDR6864	43	385 (35)	252 (46)	49 (33)			3.3 (46.1)	2.5 (0.5 : 4.1)
10	Arm	BDR6864	42	371 (32)	268 (41)	57 (38)			2.8 (32.8)	2.0 (0.5 : 5.0)
10	50 µg/ml	BEQ11094	90	352 (37)	282 (44)	83 (42)	28 (41)	68 (41)	1.7 (27.2)	1.5 (0.4 : 3.0)
10	100 µg/ml (1st replicate)	BEQ11094	90	400 (41)	328 (47)	90 (44)	25 (41)	61 (35)	1.7 (34.3)	1.5 (1.0 : 3.0)
10	100 µg/ml (2nd replicate)	BEQ11094	90	410 (37)	349 (42)	96 (36)	24 (39)	59 (32)	1.7 (28.3)	1.5 (0.5 : 3.0)
20		PDY11431	23	609 (30)	536 (34)	97 (47)	33 (30)	121 (39)	2.5 (25.2)	2.0 (1.0 : 4.0)
20		PDY11941	17	677 (26)	579 (33)	132 (33)	30 (23)	91 (36)	2.2 (28.0)	1.5 (1.0 : 3.0)
20	Young	POP11814	18	716 (38)	671 (40)	171 (28)	28 (51)	70 (45)	1.7 (21.5)	1.5 (0.5 : 3.0)
20	Elderly	POP11814	18	970 (42)	891 (41)	166 (27)	21 (53)	82 (36)	2.8 (21.5)	1.8 (1.0 : 3.0)
20		PDY11824	20	627 (33)	573 (35)	130 (44)	32 (35)	95 (49)	2.1 (20)	2.0 (1.0 : 3.0)

AUC=Area under the concentration versus time curve extrapolated to infinity, AUC_{last}=Area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to the last significant (ie. >LLOQ) plasma concentration, CL/F=Apparent total body clearance, C_{max}=Maximum plasma concentration observed, CV=Coefficient of variation, t_{1/2z}=Apparent terminal half-life, t_{max}=Time to maximum plasma concentration, V_z/F=Apparent volume of distribution during terminal phase

^a Maximum number of subjects per treatment group. Numbers of subjects may vary for individual parameters.

(source: Lixisenatide Investigator's Brochure; Table 10, page 62)

Table 9 Pharmacokinetic parameters of lixisenatide after single subcutaneous doses from 5 µg to 20 µg in T2DM patients.

Dose (µg)	Study	N ^a	Geometric mean (%CV)						Median (range)	
			AUC (pg.h/mL)	AUClast (pg.h/mL)	Cmax (pg/mL)	CL/F (L/h)	Vz/F (L)	t1/2z (h)	tmax (h)	
5	Caucasian / White	PDY6797	7	175 (NC)	79 (45)	24 (31)	29 (NC)	109 (NC)	4.1 (71.5)	2.5 (1.5 : 3.5)
5	Japanese / Asian	PDY6797	11	253 (37)	92 (71)	30 (43)	20 (38)	69 (9)	3.7 (83.7)	1.5 (1.0 : 2.0)
10	Caucasian / White	PDY6797	13	365 (33)	177 (64)	47 (56)	27 (36)	92 (38)	2.9 (40.7)	2.0 (0.0 : 4.5)
10	Japanese / Asian	PDY6797	9	264 (55)	230 (56)	62 (36)	38 (61)	96 (46)	2.0 (61.6)	1.5 (0.6 : 3.5)
20		PDY10433	21	503 (31)	424 (33)	82 (25)	40 (37)	139 (30)	2.5 (26.7)	2.0 (1.0 : 4.0)

Single-dose PK studies in patients with type 2 diabetes included: PDY10433, PDY6797

AUC=Area under the concentration versus time curve extrapolated to infinity, AUClast=Area under the plasma concentration versus time curve for

time 0 to the last significant (>LOQ) plasma concentration, CL/F=Apparent total body clearance, Cmax=Maximum plasma concentration observed, CV=Coefficient of variation,

NC = Not possible to calculate, t1/2z=Apparent terminal elimination half-life, tmax=Time to maximum plasma concentration, Vz/F=Volume of distribution

^a Maximum number of subjects per treatment group. Number of subjects may vary for individual parameters.

(source: *Lixisenatide Investigator's Brochure; Table 12, page 64*)

2.3.1.2 Multiple Once Daily Doses

Multiple-dose pharmacokinetics of lixisenatide in healthy subjects are available from 8 multiple dose studies across a dose range of 10 µg QD to 30 µg BID (INT10408, INT10409, INT10782, INT10783, POP11320, TDR11215, TES6865, and TES11807). Since the presence of anti-lixisenatide antibodies increases the concentrations of total lixisenatide measured in plasma as well as the variability in derived PK parameters, the sponsor chose to describe the PK profile in healthy subjects after multiple dose administration of lixisenatide primarily by data from antibody-negative subjects. Multiple dose data for the plasma PK of lixisenatide in patients with T2DM are available from 3 studies across a dose range of 5 µg QD to 30 µg BID (ACT6011, DRI6012, PDY6797).

After multiple dose administration, the extent of absorption was dose proportional in healthy subjects between dose levels of 10 and 20 µg QD, and in patients with T2DM between dose levels of 5 to 30 µg QD and BID.

There was no clear relationship between lixisenatide dose levels and mean elimination half-life values. At steady state, the mean apparent total body clearance (CL/F) of lixisenatide ranged between 29 and 64 L/h in healthy subjects, and between 20 and 67 L/h in patients with T2DM, with no consistent trends across dose levels.

Representative mean plasma concentration-time profiles of lixisenatide following multiple-dose are illustrated in [Figure 4](#) below.

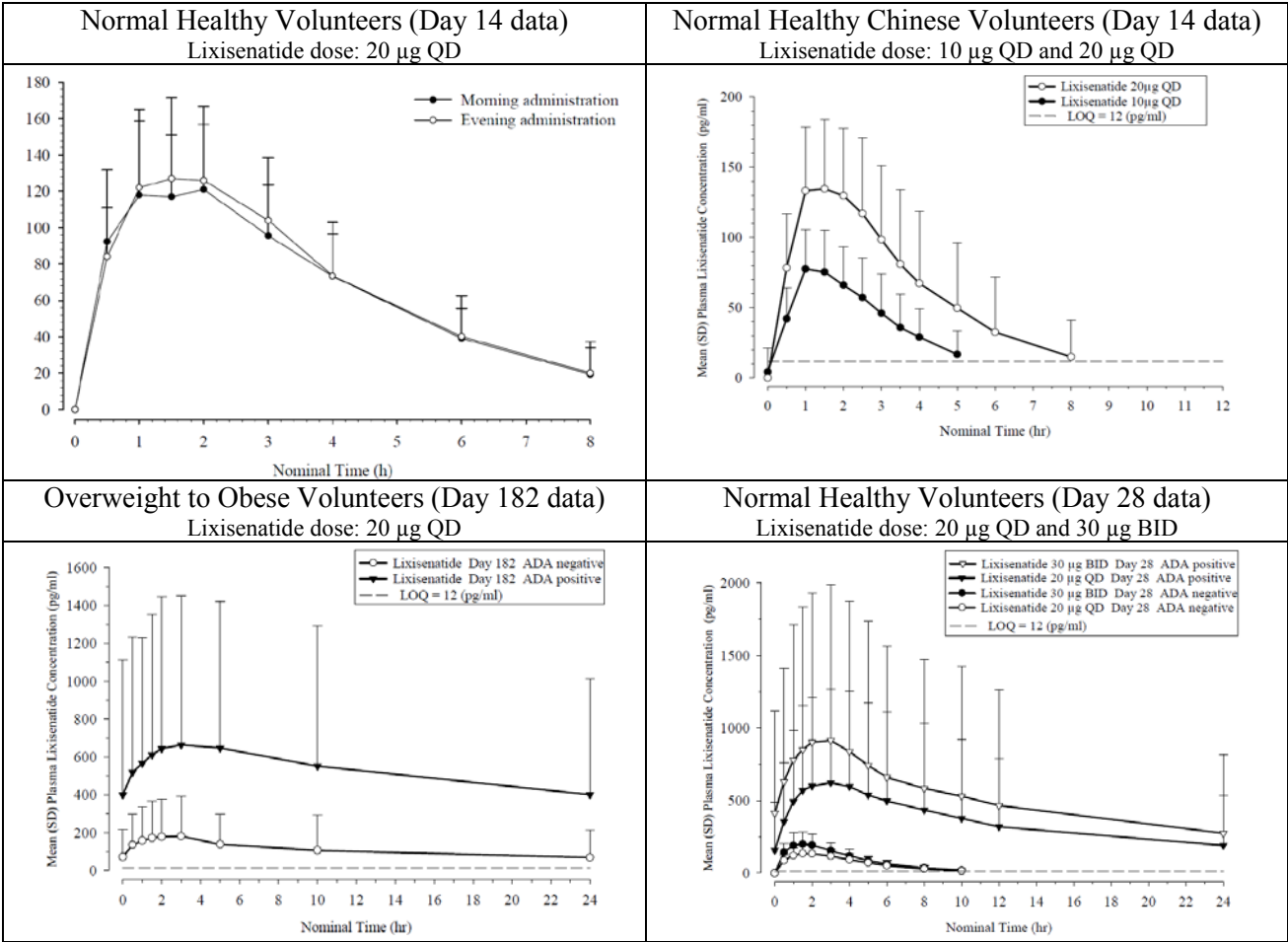


Figure 4 Mean plasma concentration time profile of lixisenatide after multiple SC doses of 10 µg, 20 µg or 30 µg

(Source: Study INT10409, Figure 7, Page 74; Study POP11320, Figure 2, Page 52; Study TDR11215, Figure 8, Page 121; Study TES11807, Figure 14, Page 131)

The mean and SD of pharmacokinetic parameters for lixisenatide across the multiple-dose studies are presented in [Tables 10](#) and [11](#) below.

Table 10 Pharmacokinetic parameters of lixisenatide after multiple subcutaneous doses from 10 µg to 30 µg in healthy subjects.

Dose (µg)	Study	N ^a	Geometric mean (%CV)					Median (range)	
			AUC _{tau} ^b (pg.h/mL)	AUC _{last} (pg.h/mL)	C _{max} (pg/mL)	CL _{ss} /F (L/h)	t _{1/2z} (h)	t _{max} (h)	
10	QD Day 7	POP11320	14	261 (97)	247 (105)	80 (35)	38 (51)	1.4 (30.7)	1.3 (0.5 : 2.5)
20	QD Day 14	POP11320	14	547 (29)	539 (47)	154 (28)	37 (27)	1.7 (29.7)	1.5 (1.0 : 3.0)
20	QD Day 11	INT10408	9	444 (36)	416 (37)	104 (26)	45 (52)	2.0 (24.9)	1.5 (1.0 : 2.0)
20	QD Day 14/15 - atorv a.m.	INT10409	9	643 (35)	620 (34)	154 (17)	31 (23)	2.1 (23.5)	1.5 (1.0 : 3.0)
20	QD Day 14/15 - atorv p.m.	INT10409	9	645 (33)	613 (33)	136 (33)	31 (36)	2.2 (26.2)	1.5 (1.0 : 2.0)
20	QD Day 14	INT10782	15	602 (31)	545 (32)	132 (27)	33 (38)	2.3 (191.4)	1.5 (0.5 : 3.0)
20	QD Day 17	INT10783	15	608 (68)	543 (74)	128 (52)	33 (43)	2.0 (20.4)	2.0 (1.0 : 4.0)
20	QD Day 28	TES6865	15	311 (49)	294 (51)	78 (51)	64 (51)	2.2 (32.4)	1.0 (0.5 : 2.0)
30	BID Day 28	TES6865	15	808 (33)	816 (34)	174 (36)	37 (39)	2.5 (23.2)	1.5 (1.0 : 3.0)
20	QD Day 28	TES11807	32	700 (47)	642 (47)	134 (39)	29 (40)	2.2 (22)	1.5 (1.0 : 5.0)
30	BID Day 28	TES11807	28	911 (33)	922 (35)	195 (42)	33 (34)	2.5 (18)	1.5 (0.5 : 3.0)
20	QD Day 8	TDR11215	127	478 (38)	317 (53)	73 (44)	-	3.5 (63)	1.6 (0.0 : 5.0)
20	QD Day 182	TDR11215	26	1350 (147)	1030 (159)	139 (106)	-	8.4 (283)	3.0 (0.5 : 5.0)

AUC=Area under the concentration versus time curve extrapolated to infinity, AUC_{last}=Area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to the last significant (ie, >LLOQ) plasma concentration, CL_{ss}/F=Apparent total body clearance at steady state, C_{max}=Maximum plasma concentration observed, CV= Coefficient of variation, t_{1/2z}=Apparent terminal half-life, t_{max}=Time to maximum plasma concentration

^a Maximum number of subjects per treatment group. Numbers of subjects may vary for individual parameters.

^b For Studies INT10408, INT10409, INT10782, INT10783, POP11320, TDR11215 and for TES6865 and TES11807 QD the AUC_{tau} was defined as AUC_(0-24h).

For Study TES6865 and TES11807 BID as AUC_(0-10h).

QD=once a day, BID=twice a day, atorv=atorvastatin

(source: Lixisenatide Investigator's Brochure; Table 11, page 63)

Table 11 Pharmacokinetic parameters of lixisenatide after multiple subcutaneous doses from 10 µg to 30 µg in T2DM patients.

Dose (µg)	Treatment group ^a	Study	N ^b	Geometric mean (%CV)					Median (range)
				AUC _{tau} (pg.h/mL)	AUC _{last} (pg.h/mL)	C _{max} (pg/mL)	CL/F (L/h)	t _{1/2z} (h)	t _{max} (h)
5	QD	ACT6011	9	241 (48)	177 (48)	35 (32)	21 (54)	3.9 (75.1)	1.3 (0.8 : 1.3)
5	QD	DRI6012	5	90 (4)	-	28 (10)	-	-	2.6 (1.3 : 4.5)
5	BID	ACT6011	11	491 (30)	448 (33)	48 (34)	20 (34)	4.1 (48.2)	2.3 (0.8 : 14.3)
5	BID	DRI6012	5	108 (25)	-	35 (21)	-	-	3.5 (1.5 : 4.5)
10	QD	ACT6011	9	384 (42)	330 (48)	76 (45)	26 (51)	2.8 (43.8)	1.3 (0.8 : 1.8)
10	QD	DRI6012	13	175 (52)	-	52 (49)	-	-	2.0 (0.4 : 3.6)
10	QD - Caucasian / White	PDY6797	16	289 (49)	-	55 (51)	35 (65)	3.3 (67.7)	2.5 (1.0 : 3.5)
10	QD - Japanese / Asian	PDY6797	20	340 (38)	-	76 (31)	29 (51)	2.1 (27.4)	1.5 (0.5 : 2.5)
10	BID	ACT6011	11	887 (27)	846 (30)	106 (22)	22 (27)	3.4 (38.6)	2.3 (1.3 : 11.3)
10	BID	DRI6012	6	211 (47)	-	58 (42)	-	-	1.9 (0.9 : 3.5)
10	BID - Caucasian / White	PDY6797	17	175 (73)	-	40 (56)	57 (116)	4.5 (71.5)	2.0 (0.0 : 3.5)
10	BID - Japanese / Asian	PDY6797	18	285 (51)	-	67 (45)	35 (100)	2.6 (33.6)	1.5 (0.5 : 2.5)
20	QD	ACT6011	9	794 (40)	752 (44)	175 (37)	24 (38)	3.1 (65.1)	1.3 (0.8 : 2.3)
20	QD	DRI6012	11	298 (36)	-	108 (39)	-	-	2.5 (0.6 : 3.9)
20	QD - Caucasian / White	PDY6797	14	691 (113)	-	108 (89)	29 (62)	3.0 (18.3)	2.5 (1.5 : 3.5)
20	QD - Japanese / Asian	PDY6797	16	785 (47)	-	163 (36)	25 (45)	2.4 (21.5)	1.8 (0.5 : 2.5)
20	BID	ACT6011	11	1658 (40)	1633 (41)	219 (39)	24 (46)	2.6 (37.1)	1.3 (0.8 : 13.3)
20	BID	DRI6012	4	517 (68)	-	155 (74)	-	-	1.0 (0.4 : 2.5)
20	BID - Caucasian / White	PDY6797	16	526 (38)	-	90 (37)	38 (55)	3.0 (26.3)	2.0 (0.5 : 2.5)
20	BID - Japanese / Asian	PDY6797	16	588 (46)	-	125 (57)	34 (59)	2.6 (29.1)	1.5 (0.0 : 4.5)
30	QD	DRI6012	7	406 (37)	-	116 (37)	-	-	1.0 (0.9 : 2.5)
30	QD - Caucasian / White	PDY6797	8	447 (61)	-	84 (44)	67 (104)	2.7 (30.3)	3.0 (1.5 : 3.5)
30	QD - Japanese / Asian	PDY6797	9	1052 (31)	-	188 (28)	29 (36)	3.0 (21.6)	1.5 (0.9 : 2.5)

Dose (μ g)	Treatment group ^a	Study	N ^b	Geometric mean (%CV)					Median (range)
				AUC _{tau} (pg.h/mL)	AUC _{last} (pg.h/mL)	C _{max} (pg/mL)	CL/F (L/h)	t _{1/2z} (h)	t _{max} (h)
30	BID	DRI6012	2	584 (24)	-	179 (10)	-	-	1.3 (1.0 : 1.6)
30	BID - Caucasian / White	PDY6797	13	840 (37)	-	144 (34)	36 (41)	3.0 (26.1)	1.5 (1.0 : 3.5)
30	BID - Japanese / Asian	PDY6797	10	878 (23)	-	175 (35)	34 (23)	2.6 (18.9)	1.5 (0.5 : 2.5)

Multiple-dose PK studies in patients with type 2 diabetes included: ACT6011, DRI6012, PDY6797

AUC_{last}=Area under the plasma concentration versus time curve for time 0 to the last significant (>LOQ) plasma concentration, AUC_{tau}=Area under the plasma concentration versus time curve for the specified dosing interval, for study ACT6011 QD/BID as 0:14h-23:55h, for study DRI6012 as 0h-4.5h, for study PDY6797 QD as 0h-24h and for study PDY6797 BID as 0h-10h

CL/F=Apparent total body clearance, C_{max}=Maximum plasma concentration observed, CV=Coefficient of variation, t_{1/2z}=Apparent terminal elimination half-life,

t_{max}=Time to maximum plasma concentration

^a QD=once a day, BID=twice a day

^b Maximum number of subjects per treatment group. Number of subjects may vary for individual parameters.

In Study ACT6011, data for the 5, 10, and 20 μ g dose levels in anti-lixisenatide antibody negative patients were obtained using a bioanalytical method that measured plasma concentrations of unbound (= free) lixisenatide. In all other studies, data were obtained using a bioanalytical method that measured plasma concentrations of total lixisenatide.

(source: Lixisenatide Investigator's Brochure; Table 13, page 65)

2.3.2 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Pharmacokinetic evaluation following stepwise increases in lixisenatide of up to 20 µg QD or BID showed that the area under the concentration-time curve (AUC) and C_{max} increased with increasing doses of lixisenatide. In the anti-lixisenatide antibody-negative patients, dose-proportionality was seen within the QD and BID dosing regimens studied and the AUC value doubled for BID dosing as compared to QD dosing. The apparent terminal half-life ($t_{1/2z}$) for lixisenatide was approximately 3 to 4 hours. In the anti-lixisenatide antibody-positive patients, the magnitude and variability of exposure increased and the elimination half-life was around 8 to 10 hours.

Representative plot and data are shown in [Figure 5](#) and [Table 12](#), respectively.

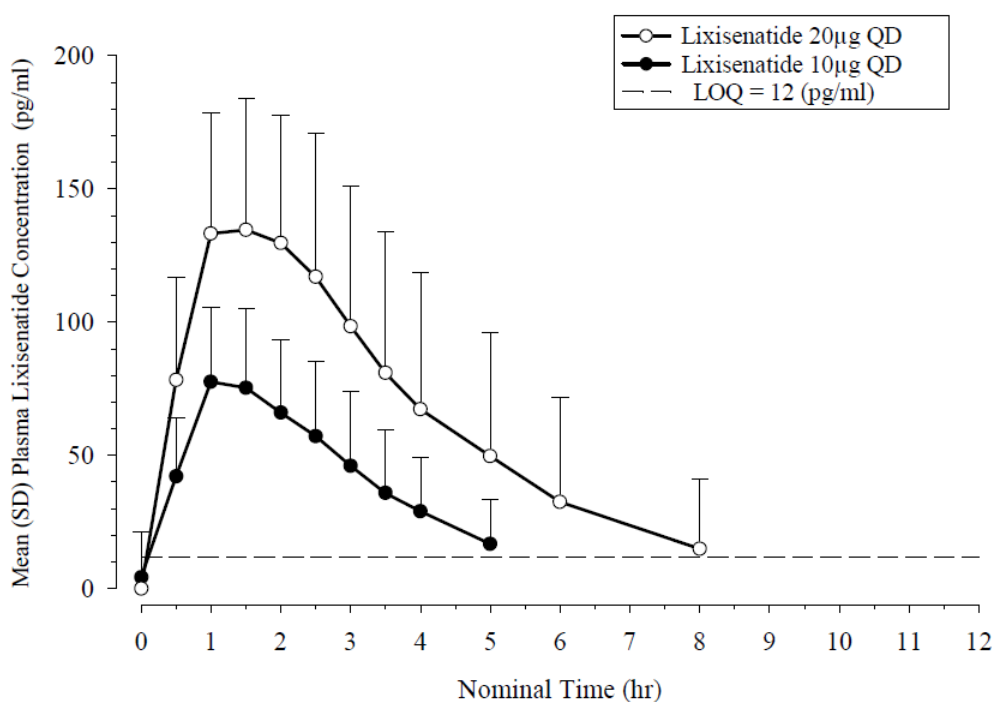


Figure 5 Mean plasma concentration time profile of lixisenatide after multiple SC doses of 10 µg and 20 µg

(source: sponsor's study pop11320; Figure 1, page 52)

Table 12 Pharmacokinetic parameters of lixisenatide after multiple subcutaneous doses of 10 µg and 20 µg in healthy Chinese subjects.

'Mean ± SD (CV%) [Geometric Mean] N	Plasma Lixisenatide	
	Lixisenatide 10µg QD	Lixisenatide 20µg QD
	Day 7	Day 14
C_{max} (pg/ml)	83.2 ± 28.0 (33.6) [78.6]	156 ± 51.1 (32.8) [148]
t_{max}^a (hr)	1.00 (0.50 - 2.50)	1.50 (1.00 - 3.00)
AUC_T (pg·hr/ml)	317 ± 276 (87.0) [261] ^b	588 ± 348 (59.1) [531] ^c
$t_{1/2z}$ (hr)	1.60 ± 0.503 (31.4) [1.53] ^b	1.81 ± 0.509 (28.1) [1.75] ^c

^a Median
(Min - Max)

^b n=19, Subject 156001004, 156001020 not included in calculation of summary statistics

^c n=20, Subject 156001020 not included in calculation of summary statistics

(source: sponsor's study pop11320; Table 13, page 53)

2.3.3 What are the pharmacodynamic characteristics of lixisenatide after subcutaneous administration and how do they relate to the dose?

Sponsor evaluated lixisenatide's insulintropic effects by assessing (a) change from baseline to Day 4 in the postprandial blood glucose AUC, (b) change from baseline to Day 4 in fasting blood glucose, (c) change from baseline to Day 4 in average 7-point blood glucose profile, (d) change from baseline to Day 29 in HbA_{1c}, (e) change from baseline to Day 4 in the HOMA insulin sensitivity parameters – Beta cell function, and Insulin resistance, in a pharmacodynamic safety and tolerability study in T2DM patients (study ACT6011). In this placebo controlled study, the starting dose of lixisenatide was 5 µg per s.c. injection (administered either QD or BID). The dose per injection was increased every 5th day in increments of 2.5 µg (Table 13), up to a maximum level of 20 µg during the last 4 days (Days 25 to 28) in those subjects who tolerated the dose and lixisenatide was safe. The morning injections were administered s.c. 15 min before breakfast, and the evening injections were administered 10 hours after the morning injection, 15 min before dinner.

Table 13 Planned Dosing of Lixisenatide or Placebo

Planned treatment days	Dose per injection	Daily dose at QD regimen	Daily dose at BID regimen
Day 1 – Day 4	5.0 µg AVE0010	5.0 µg AVE0010	10.0 µg AVE0010
Day 5 – Day 8	7.5 µg AVE0010	7.5 µg AVE0010	15.0 µg AVE0010
Day 9 – Day 12	10.0 µg AVE0010	10.0 µg AVE0010	20.0 µg AVE0010
Day 13 – Day 16	12.5 µg AVE0010	12.5 µg AVE0010	25.0 µg AVE0010
Day 17 – Day 20	15.0 µg AVE0010	15.0 µg AVE0010	30.0 µg AVE0010
Day 21 – Day 24	17.5 µg AVE0010	17.5 µg AVE0010	35.0 µg AVE0010
Day 25 – Day 28	20.0 µg AVE0010	20.0 µg AVE0010	40.0 µg AVE0010

The following PD variables were evaluated in this study:

- The AUC_[0:14h-4:55h] for postprandial blood glucose determined for the breakfast, lunch and dinner test meal on the 4th day of each dose level;
- The AUC_[0:14h-4:55h] for the postprandial changes in blood glucose relative to the pre-meal value determined for the breakfast, lunch and dinner test meal at baseline (Day -1) and on the 4th day of each dose level;
- The morning fasting blood glucose levels on the 3rd and 4th day of each dose level;
- Average 7-point daily blood glucose profile: The mean of the blood glucose measurements before meals (at 0:14h, 5:14h, 10:14h after the morning injection), 90 minutes after meals (at 1:45h, 6:45h, 11:45h after the morning injection), and at bedtime (at 14:55h after the morning injection);
- Maximum postprandial blood glucose after breakfast, lunch and dinner;
- The AUC_[0:14h-4:55h] for the postprandial changes relative to the pre-meal value in insulin, C-peptide, and glucagon levels for the test breakfast at baseline (Day -1), on Day 4, on the 4th day of the 10 µg dose level, and on Day 28;
- HbA_{1c} measured on Day 29;
- Insulin sensitivity: The following parameters from the HOMA were analyzed:
 - Beta cell function = $[20 \times \text{fasting insulin } (\mu\text{IU/mL})] / [\text{fasting glucose (mmol/L)} - 3.5]$,
 - Insulin resistance = $[\text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glucose (mmol/L)}] / 22.5$;
- Gastric emptying time (from a ¹³C-octanoic acid breath test) for the test breakfast meal on the 4th day of the 10 µg dose level and on Day 28. The following parameters were collected:
 - Lag phase t_{lag},
 - Emptying half-life t_{1/2},
 - Gastric emptying coefficient (GEC).

Postprandial changes in blood glucose AUC relative to baseline

The primary analysis variable in this trial was the area under the blood glucose concentration time curve from 0:14 h after the morning injection (administered just before standardized breakfast intake) until 4:55 h after the morning injection (AUC_[0:14h-4:55h]) on the 4th day of the highest individually well-tolerated dose. The change compared to baseline (Day -1) was evaluated, as summarized in [Table 14](#) below.

Table 14 Change from baseline in the postprandial blood glucose AUC at breakfast on the 4th day of the highest well-tolerated dose (mITT population)

Treatment group	N	Adjusted mean ± SE			95% CI of difference	p-value
		Baseline mean (h.mg/dL)	Change from baseline	Difference vs. placebo		
Placebo	22	1007.4 ± 38.18	3.0 ± 44.62	--	--	--
AVE0010 QD	21	947.6 ± 39.08	-378.3 ± 44.58	-381.3 ± 62.92	(-507.1; -255.4)	<0.0001
AVE0010 BID	21	863.6 ± 39.08	-360.0 ± 45.97	-362.9 ± 65.75	(-494.5; -231.4)	<0.0001

Differences vs. placebo are calculated as AVE0010 minus placebo.

CI = confidence interval; mITT = modified intention-to-treat; N = number of evaluable subjects; SE = standard error.

(source: sponsor's study ACT6011; Table 20, page 94)

Significant differences in postprandial glucose were observed compared to placebo in the lixisenatide QD and BID dose groups. The mean baseline blood glucose AUC was highest in the placebo group (1007.4 h.mg/dL), which then increased slightly by 3.0 h.mg/dL by the 4th day of treatment. In contrast, in the lixisenatide groups, which had lower baseline AUC values (974.6 h.mg/dL in the QD group, and 863.6 h.mg/dL in the BID group), decreases of -378.3 and -360.0 h.mg/dL were observed, respectively, by the 4th day of treatment.

There were no statistically significant differences between the lixisenatide QD and BID groups.

Mean profiles of blood glucose levels across the day at baseline and at the highest well-tolerated dose are shown in [Figures 6, 7](#) and [8](#) below for the 3 treatment groups. Compared to placebo, clear reductions in blood glucose levels were seen after breakfast with QD dosing of lixisenatide, and after breakfast and dinner with BID dosing of lixisenatide.

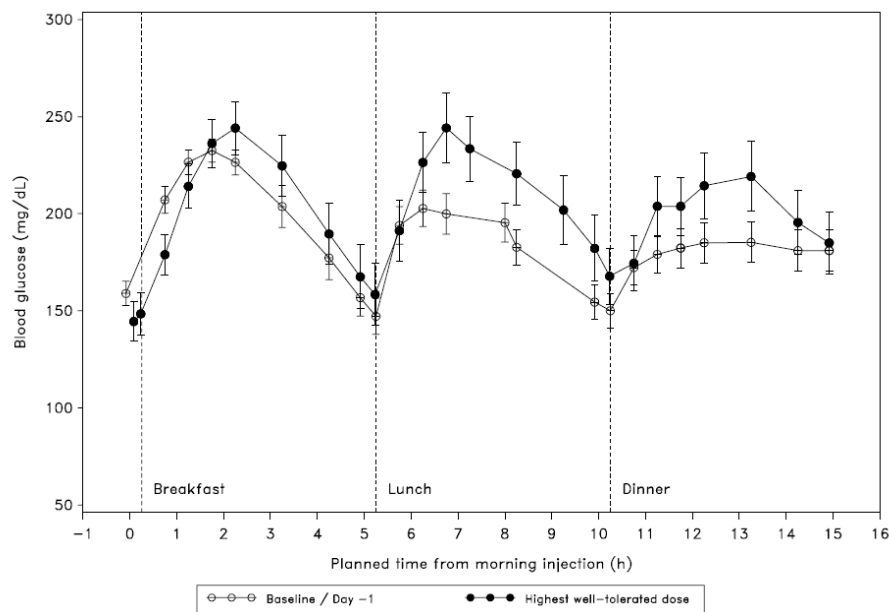


Figure 6 Mean ± SE blood glucose values in the placebo group at baseline and at the highest well tolerated dose (mITT population)

(source: sponsor's study ACT6011; Figure 5, page 95)

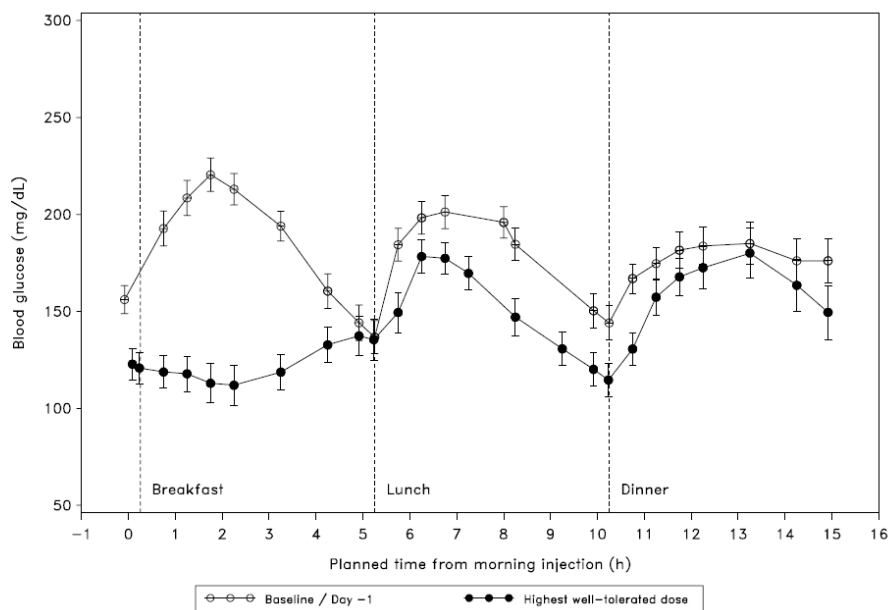


Figure 7 Mean $\pm$ SE blood glucose values in the lixisenatide QD group at baseline and at the highest well-tolerated dose (mITT population)

(source: sponsor's study ACT6011; Figure 6, page 95)

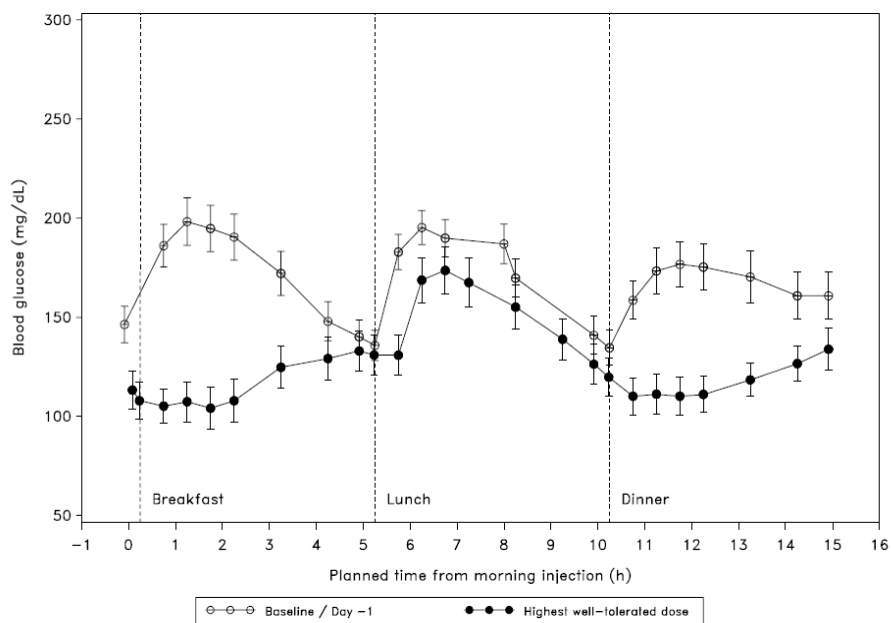


Figure 8 Mean $\pm$ SE blood glucose values in the lixisenatide BID group at baseline and at the highest well-tolerated dose (mITT population)

(source: sponsor's study ACT6011; Figure 7, page 96)

Analyses of the changes from baseline in the postprandial blood glucose AUC at breakfast, lunch, and dinner on the 4th day of the 10 and 20 μ g dose levels, and at the highest individually well tolerated dose, are summarized in [Table 15](#) below:

Table 15 Change from baseline in the postprandial blood glucose AUC at breakfast, lunch, and dinner (mITT population)

MEAL Treatment group Dose level (µg)	N	Adjusted mean ± SE			95% CI of difference	p-value
		Baseline mean (h.mg/dL)	Change from baseline	Difference vs. placebo		
BREAKFAST						
Placebo						
10.0	22	1007.4 ± 38.18	-51.4 ± 36.12	--	--	--
20.0	22	1007.4 ± 38.18	-0.4 ± 45.35	--	--	--
Highest individually well-tolerated dose	22	1007.4 ± 38.18	3.0 ± 44.62	--	--	--
AVE0010 QD						
10.0	21	947.6 ± 39.08	-346.7 ± 36.09	-295.3 ± 50.93	(-397.2; -193.5)	<0.0001
20.0	19	947.6 ± 39.08	-387.4 ± 47.83	-387.0 ± 65.50	(-518.1; -255.9)	<0.0001
Highest individually well-tolerated dose	21	947.6 ± 39.08	-378.3 ± 44.58	-381.3 ± 62.92	(-507.1; -255.4)	<0.0001
AVE0010 BID						
10.0	21	863.6 ± 39.08	-316.7 ± 37.21	-265.3 ± 53.23	(-371.8; -158.9)	<0.0001
20.0	21	863.6 ± 39.08	-361.3 ± 47.08	-360.9 ± 67.12	(-495.3; -226.6)	<0.0001
Highest individually well-tolerated dose	21	863.6 ± 39.08	-360.0 ± 45.97	-362.9 ± 65.75	(-494.5; -231.4)	<0.0001
LUNCH						
Placebo						
10.0	22	905.0 ± 40.04	-0.4 ± 39.53	--	--	--
20.0	22	905.0 ± 40.04	102.9 ± 52.28	--	--	--
Highest individually well-tolerated dose	22	905.0 ± 40.04	103.2 ± 52.14	--	--	--
AVE0010 QD						
10.0	21	890.0 ± 40.98	-204.4 ± 40.36	-204.0 ± 56.44	(-316.9; -91.2)	0.0006
20.0	19	890.0 ± 40.98	-186.1 ± 56.21	-289.0 ± 76.64	(-442.4; -135.6)	0.0004
Highest individually well-tolerated dose	21	890.0 ± 40.98	-174.3 ± 53.24	-277.5 ± 74.44	(-426.4; -128.6)	0.0004
AVE0010 BID						
10.0	21	848.4 ± 40.98	-95.7 ± 40.56	-95.3 ± 56.86	(-209.1; 18.4)	0.0988
20.0	21	848.4 ± 40.98	-144.5 ± 53.75	-247.4 ± 75.26	(-398.0; -96.7)	0.0017
Highest individually well-tolerated dose	21	848.4 ± 40.98	-152.9 ± 53.50	-256.1 ± 74.99	(-406.1; -106.1)	0.0011

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MEAL Treatment group Dose level (µg)	N	Adjusted mean ± SE			95% CI of difference	p-value
		Baseline mean (h.mg/dL)	Change from baseline	Difference vs. placebo		
DINNER						
Placebo						
10.0	22	889.9 ± 47.76	-42.0 ± 36.41	--	--	--
20.0	22	889.9 ± 47.76	66.7 ± 49.75	--	--	--
Highest individually well-tolerated dose	22	889.9 ± 47.76	64.0 ± 50.67	--	--	--
AVE0010 QD						
10.0	21	875.2 ± 48.88	-139.0 ± 37.19	-97.0 ± 51.98	(-201.0; 7.0)	0.0670
20.0	19	875.2 ± 48.88	-133.0 ± 53.45	-199.7 ± 72.93	(-345.7; -53.7)	0.0082
Highest individually well-tolerated dose	21	875.2 ± 48.88	-115.1 ± 51.76	-179.1 ± 72.35	(-323.8; -34.4)	0.0162
AVE0010 BID						
10.0	21	823.3 ± 48.88	-224.0 ± 37.37	-182.0 ± 52.36	(-286.7; -77.3)	0.0010
20.0	21	823.3 ± 48.88	-280.9 ± 51.10	-347.6 ± 71.58	(-490.9; -204.4)	<0.0001
Highest individually well-tolerated dose	21	823.3 ± 48.88	-293.6 ± 52.01	-357.5 ± 72.88	(-503.3; -211.8)	<0.0001

Differences vs. placebo are calculated as AVE0010 minus placebo.
CI = confidence interval; mITT = modified intention-to-treat; N = number of evaluable subjects; SE = standard error.

(source: sponsor's study ACT6011; Table 21, page 97)

Baseline AUC values were highest in the placebo group at all three meal times, but only the difference between the baseline values for the placebo (1007.4 h.mg/dL) and the lixisenatide BID (863.6 h.mg/dL) groups at breakfast was statistically significant (p = 0.0107).

The placebo-adjusted change from baseline in the postprandial blood glucose AUC were significant at all dose levels for the meals at which lixisenatide had been administered, i.e., at breakfast for the lixisenatide QD group, and at breakfast and dinner for the lixisenatide BID group.

In addition, at lunch the placebo-adjusted change from baseline in the postprandial blood glucose AUC were significant at all dose levels for the lixisenatide QD group, and in the lixisenatide BID group the differences to placebo were statistically significant for dose levels of 12.5 µg and higher. At dinner, the differences to placebo were statistically significant in the lixisenatide QD group at all dose levels apart from 5 and 10 µg.

Postprandial changes in blood glucose AUC relative to pre-meal values

Analyses of the postprandial changes in blood glucose AUC relative to pre-meal values at breakfast, lunch, and dinner on the 4th day of each dose level are summarized in [Table 16](#) below.

Table 16 Postprandial changes in blood glucose AUC relative to pre-meal values on the 4th day of each dose level at breakfast, lunch, and dinner (mITT population)

MEAL Treatment group Dose level (µg)	N	Adjusted mean ± SE			95% CI of difference	p-value
		Baseline mean (h.mg/dL)	Change from baseline	Difference vs. placebo		
BREAKFAST						
Placebo						
10.0	22	212.7 ± 22.89	187.9 ± 20.10	--	--	--
20.0	22	212.7 ± 22.89	257.7 ± 23.20	--	--	--
Highest individually well-tolerated dose	22	212.7 ± 22.89	258.3 ± 23.55	--	--	--
AVE0010 QD						
10.0	21	161.4 ± 23.43	-3.5 ± 20.00	-191.3 ± 28.49	(-248.3; -134.3)	<0.0001
20.0	19	161.4 ± 23.43	7.5 ± 24.32	-250.3 ± 33.67	(-317.7; -182.9)	<0.0001
Highest individually well-tolerated dose	21	161.4 ± 23.43	4.2 ± 23.44	-254.0 ± 33.40	(-320.8; -187.2)	<0.0001
AVE0010 BID						
10.0	21	131.2 ± 23.43	29.1 ± 20.41	-158.7 ± 29.32	(-217.4; -100.1)	<0.0001
20.0	21	131.2 ± 23.43	60.0 ± 23.69	-197.8 ± 33.95	(-265.7; -129.8)	<0.0001
Highest individually well-tolerated dose	21	131.2 ± 23.43	57.4 ± 23.92	-200.8 ± 34.36	(-269.6; -132.1)	<0.0001
LUNCH						
Placebo						
10.0	22	119.2 ± 34.33	228.7 ± 31.20	--	--	--
20.0	22	119.2 ± 34.33	267.5 ± 26.59	--	--	--
Highest individually well-tolerated dose	22	119.2 ± 34.33	261.4 ± 26.88	--	--	--
AVE0010 QD						
10.0	21	169.7 ± 35.14	133.2 ± 31.91	-95.4 ± 44.82	(-185.1; -5.8)	0.0373
20.0	19	169.7 ± 35.14	66.3 ± 28.57	-201.2 ± 39.11	(-279.4; -122.9)	<0.0001
Highest individually well-tolerated dose	21	169.7 ± 35.14	72.7 ± 27.49	-188.7 ± 38.61	(-265.9; -111.4)	<0.0001
AVE0010 BID						
10.0	21	147.4 ± 35.14	187.3 ± 31.78	-41.4 ± 44.55	(-130.5; 47.7)	0.3566
20.0	21	147.4 ± 35.14	75.7 ± 27.15	-191.8 ± 38.04	(-267.9; -115.6)	<0.0001
Highest individually well-tolerated dose	21	147.4 ± 35.14	96.4 ± 27.38	-165.0 ± 38.38	(-241.8; -88.3)	0.0001

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MEAL Treatment group Dose level (µg)	N	Adjusted mean ± SE			95% CI of difference	p-value
		Baseline mean (h.mg/dL)	Change from baseline	Difference vs. placebo		
DINNER						
Placebo						
10.0	22	117.5 ± 33.05	128.2 ± 22.94	--	--	--
20.0	22	117.5 ± 33.05	151.4 ± 20.86	--	--	--
Highest individually well-tolerated dose	22	117.5 ± 33.05	155.7 ± 19.25	--	--	--
AVE0010 QD						
10.0	21	123.3 ± 33.83	164.2 ± 23.48	36.0 ± 32.83	(-29.7; 101.7)	0.2772
20.0	19	123.3 ± 33.83	221.7 ± 22.44	70.4 ± 30.64	(9.0; 131.7)	0.0253
Highest individually well-tolerated dose	21	123.3 ± 33.83	216.4 ± 19.70	60.7 ± 27.55	(5.6; 115.8)	0.0315
AVE0010 BID						
10.0	21	118.9 ± 33.83	-12.7 ± 23.48	-140.9 ± 32.82	(-206.6; -75.3)	0.0001
20.0	21	118.9 ± 33.83	11.2 ± 21.35	-140.2 ± 29.84	(-199.9; -80.4)	<0.0001
Highest individually well-tolerated dose	21	118.9 ± 33.83	-11.3 ± 19.70	-167.0 ± 27.55	(-222.1; -111.9)	<0.0001

Differences vs. placebo are calculated as AVE0010 minus placebo.
CI = confidence interval; mITT = modified intention-to-treat; N = number of evaluable subjects; SE = standard error.

(source: sponsor's study ACT6011; Table 22, page 100)

The difference between the baseline values for the placebo (212.7 h.mg/dL) and the lixisenatide BID (131.2 h.mg/dL) groups at breakfast was statistically significant (p = 0.0157).

The placebo-adjusted change in the postprandial blood glucose AUC relative to the pre-meal value were significant at all dose levels for the meals at which lixisenatide had been administered, i.e., at breakfast for the lixisenatide QD group, and at breakfast and dinner for the lixisenatide BID group.

In addition, at lunch the placebo-adjusted change in the postprandial blood glucose AUC tended to increase with dose at the higher dose levels, so that the changes were statistically significant relative to the pre-meal value at dose levels of 10 µg and above for the lixisenatide QD group and at dose levels of 12.5 µg and above for the lixisenatide BID group. At dinner, the changes were statistically significant in the lixisenatide QD group only at the highest dose levels of 20 µg and the highest individually well-tolerated dose.

There were no statistically significant differences in the blood glucose AUC values for the postprandial change relative to the pre-meal value between the lixisenatide QD and BID groups at either of the administered doses, at breakfast or lunch. However, at dinner, differences between the lixisenatide QD and BID groups were significant at each dose level, with the AUC values in the BID group being much lower than in the QD group.

Postprandial changes in insulin relative to pre-breakfast value

The analysis of the AUC_[0:14h-4:55h] after breakfast on the 4th day of treatment for the postprandial change in insulin relative to the pre-breakfast value is summarized in [Table 17](#) below

Table 17 AUC_[0:14h-4:55h] for the postprandial change in insulin after breakfast relative to the pre-breakfast value (mITT population)

Treatment group Dose level (µg)	N	Adjusted mean ± SE			95% CI of difference	p-value
		AUC at baseline (h.µIU/mL)	AUC during treatment	Difference vs. placebo		
Placebo						
10.0	21	105.5 ± 12.68	140.2 ± 12.99	--	--	--
20.0	21	105.5 ± 12.68	140.1 ± 12.81	--	--	--
Highest individually well-tolerated dose	21	105.5 ± 12.68	140.1 ± 12.81	--	--	--
AVE0010 QD						
10.0	18	98.8 ± 13.69	96.6 ± 13.90	-43.7 ± 18.90	(-81.6; -5.7)	0.0250
20.0	18	98.8 ± 13.69	83.3 ± 13.70	-56.8 ± 18.63	(-94.2; -19.4)	0.0037
Highest individually well-tolerated dose	18	98.8 ± 13.69	83.3 ± 13.70	-56.8 ± 18.63	(-94.2; -19.4)	0.0037
AVE0010 BID						
10.0	15	60.1 ± 15.00	129.4 ± 15.78	-10.9 ± 20.88	(-52.8; 31.1)	0.6050
20.0	15	60.1 ± 15.00	106.5 ± 15.55	-33.6 ± 20.58	(-74.9; 7.7)	0.1089
Highest individually well-tolerated dose	15	60.1 ± 15.00	106.5 ± 15.55	-33.6 ± 20.58	(-74.9; 7.7)	0.1089

Differences vs. placebo are calculated as AVE0010 minus placebo.

CI = confidence interval; mITT = modified intention-to-treat; N = number of evaluable subjects; SE = standard error.

(source: sponsor's study ACT6011; Table 26, page 109)

Mean baseline AUC_[0:14h-4:55h] values for insulin were lower in the lixisenatide BID group than in the placebo and lixisenatide QD groups. This trend was also observed with C-peptide and blood glucose. After breakfast on the 4th day of treatment, at all dose levels investigated, increased insulin values compared to baseline were recorded in the placebo and lixisenatide BID groups (however, from a notably lower baseline value), but not in the lixisenatide QD group. A comparison for the change from baseline in insulin AUC between lixisenatide QD group (where there was no increase in insulin AUC_[0:14h-4:55h]) and placebo (where there was an increase in AUC) showed statistical significance at all dose levels. There were no statistically significant differences between the 2 lixisenatide groups for the change from baseline in insulin AUC.

Numerically insulin secretion is higher for BID than placebo, but given the variability of the data, lixisenatide treatment given BID does not appear to be different from placebo.

Postprandial changes in C-peptide relative to pre-breakfast value

The analysis of the AUC_[0:14h-4:55h] after breakfast on the 4th day of treatment for the postprandial change in C-peptide relative to the pre-breakfast value is summarized in [Table 18](#) below.

Table 18 $AUC_{[0:14h-4:55h]}$ for the postprandial change in C-peptide after breakfast relative to the pre-breakfast value (mITT population)

Treatment group Dose level (μg)	N	Adjusted mean $\pm$ SE			95% CI of difference	p-value
		AUC at baseline (h.ng/mL)	AUC during treatment	Difference vs. placebo		
Placebo						
10.0	21	10.5 $\pm$ 0.99	14.2 $\pm$ 1.24	--	--	--
20.0	21	10.5 $\pm$ 0.99	13.5 $\pm$ 1.20	--	--	--
Highest individually well-tolerated dose	21	10.5 $\pm$ 0.99	13.5 $\pm$ 1.20	--	--	--
AVE0010 QD						
10.0	18	9.1 $\pm$ 1.06	12.7 $\pm$ 1.31	-1.5 $\pm$ 1.80	(-5.1; 2.1)	0.4178
20.0	18	9.1 $\pm$ 1.06	9.7 $\pm$ 1.27	-3.8 $\pm$ 1.74	(-7.3; -0.3)	0.0345
Highest individually well-tolerated dose	18	9.1 $\pm$ 1.06	9.7 $\pm$ 1.27	-3.8 $\pm$ 1.74	(-7.3; -0.3)	0.0345
AVE0010 BID						
10.0	17	6.7 $\pm$ 1.09	14.0 $\pm$ 1.40	-0.2 $\pm$ 1.93	(-4.1; 3.7)	0.9168
20.0	17	6.7 $\pm$ 1.09	10.7 $\pm$ 1.36	-2.8 $\pm$ 1.87	(-6.6; 0.9)	0.1366
Highest individually well-tolerated dose	17	6.7 $\pm$ 1.09	10.7 $\pm$ 1.36	-2.8 $\pm$ 1.87	(-6.6; 0.9)	0.1366

Differences vs. placebo are calculated as AVE0010 minus placebo.
 CI = confidence interval; mITT = modified intention-to-treat; N = number of evaluable subjects; SE = standard error.
 (source: sponsor's study ACT6011; Table 27, page 110)

Mean baseline $AUC_{[0:14h-4:55h]}$ values for C-peptide were lower in the lixisenatide BID group than in the placebo and lixisenatide QD groups. After breakfast on the 4th day of treatment, increased C-peptide values compared to baseline were recorded in the placebo and lixisenatide BID groups at all dose levels investigated, but in the lixisenatide QD group only at the 5 and 10 μg dose levels. Thus only the difference between lixisenatide QD and placebo for the change from baseline in C-peptide AUC at the 20 μg dose level was statistically significant. There were also no statistically significant differences between the 2 lixisenatide groups for the change from baseline in C-peptide AUC.

Consistent with the results for insulin, the highest post-treatment changes in values were also recorded in the lixisenatide BID group. Given the variability of the data, lixisenatide treatment given BID does not appear to be different from placebo.

Postprandial changes in glucagon relative to pre-breakfast value

The analysis of the $AUC_{[0:14h-4:55h]}$ after breakfast on the 4th day of treatment for the postprandial change in glucagon relative to the pre-breakfast value is summarized in [Table 19](#) below.

Table 19 AUC_[0:14h-4:55h] for the postprandial change in glucagon after breakfast relative to the pre-breakfast value (mITT population)

Treatment group Dose level (µg)	N	Adjusted mean ± SE			95% CI of difference	p-value
		AUC at baseline (h.pmol/L)	AUC during treatment	Difference vs. placebo		
Placebo						
10.0	20	14.3 ± 3.08	23.1 ± 2.51	--	--	--
20.0	20	14.3 ± 3.08	13.1 ± 3.84	--	--	--
Highest individually well-tolerated dose	20	14.3 ± 3.08	13.1 ± 3.84	--	--	--
AVE0010 QD						
10.0	17	21.3 ± 3.34	-2.8 ± 2.72	-25.9 ± 3.74	(-33.4; -18.4)	<0.0001
20.0	17	21.3 ± 3.34	-2.5 ± 4.16	-15.6 ± 5.72	(-27.1; -4.1)	0.0089
Highest individually well-tolerated dose	17	21.3 ± 3.34	-2.5 ± 4.16	-15.6 ± 5.72	(-27.1; -4.1)	0.0089
AVE0010 BID						
10.0	17	18.3 ± 3.34	1.3 ± 2.69	-21.8 ± 3.68	(-29.2; -14.4)	<0.0001
20.0	17	18.3 ± 3.34	-8.7 ± 4.11	-21.8 ± 5.64	(-33.1; -10.4)	0.0003
Highest individually well-tolerated dose	17	18.3 ± 3.34	-8.7 ± 4.11	-21.8 ± 5.64	(-33.1; -10.4)	0.0003

Differences vs. placebo are calculated as AVE0010 minus placebo.

CI = confidence interval; mITT = modified intention-to-treat; N = number of evaluable subjects; SE = standard error.

(source: sponsor's study ACT6011; Table 28, page 111)

Mean baseline AUC_[0:14h-4:55h] values for glucagon were lower in the placebo group than in the lixisenatide QD and BID groups. After breakfast on the 4th day of treatment, mean AUC values for the change relative to the pre-breakfast value for placebo increased (at the 5 and 10 µg dose levels) or remained high (at the 20 µg dose level). In contrast, in the lixisenatide QD and BID groups the glucagon AUC values decreased markedly, especially at the 10 and 20 µg dose levels, and the differences to placebo at the 10 and 20 µg dose levels were statistically significant with both regimens. There were no statistically significant differences between the 2 lixisenatide groups for the change from baseline in glucagon AUC.

The suppression of glucagon after the test breakfast in the lixisenatide groups is consistent with the known effects for GLP-1 agonists.

Changes in HbA_{1c} on Day 29 relative to baseline

The analysis of the changes in HbA_{1c} from baseline (Day -1) to Day 29 is summarized in [Table 20](#) below.

Table 20 Changes in HbA_{1c} on Day 29 relative to baseline (mITT population)

Dose level (µg)	N	Adjusted mean ± SE			95% CI of difference	p-value
		Baseline mean (%)	Change from baseline	Difference vs. placebo		
Placebo	20	8.87 ± 0.239	-0.61 ± 0.159	--	--	--
AVE0010 QD	19	8.54 ± 0.245	-1.17 ± 0.161	-0.550 ± 0.227	(-1.004; -0.096)	0.0184
AVE0010 BID	21	8.38 ± 0.233	-1.16 ± 0.154	-0.550 ± 0.223	(-0.997; -0.103)	0.0169

Differences vs. placebo are calculated as AVE0010 minus placebo.

CI = confidence interval; mITT = modified intention-to-treat; N = number of evaluable subjects; SE = standard error.

(source: sponsor's study ACT6011; Table 29, page 112)

On Day 29, there was an adjusted mean reduction in HbA_{1c} values from baseline of -1.2% in the lixisenatide QD and BID groups, compared to a reduction of -0.6% in the placebo group. The adjusted mean differences to placebo for the change from baseline in HbA_{1c} values were statistically significant for the both lixisenatide groups.

For HbA_{1c}, there was a linear relationship between values measured at baseline and on Day 29, and all subjects treated with lixisenatide achieved a decrease in HbA_{1c}, as shown in [Figure 9](#) below. Subjects on lixisenatide treatment did not experience deterioration in HbA_{1c} values.

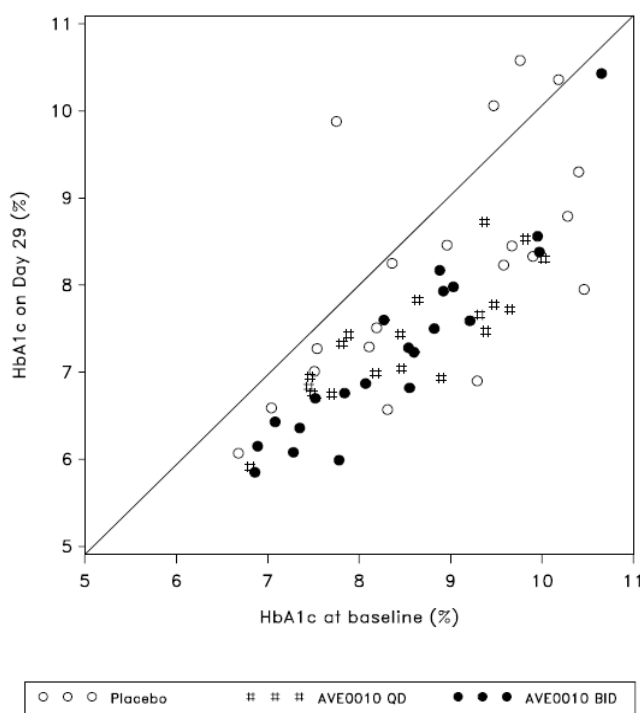


Figure 9 Scatter plot of individual HbA_{1c} values at baseline (Day -1) and on Day 29 by treatment group (mITT population)

(source: sponsor's study ACT6011; Figure 8, page 113)

Reduction of postprandial plasma glucose following 4 week treatment of 20µg lixisenatide or 1.8 mg liraglutide

A study was conducted to investigate the effects of repeated subcutaneous doses of 20 µg lixisenatide as compared to 1.8 mg liraglutide in reducing postprandial plasma glucose (PPG) assessed as area under the plasma glucose concentration curve (AUC) after a standardized breakfast at the end of a 4-week treatment period in patients with type 2 diabetes.

The schematic study design is shown in [Figure 10](#):

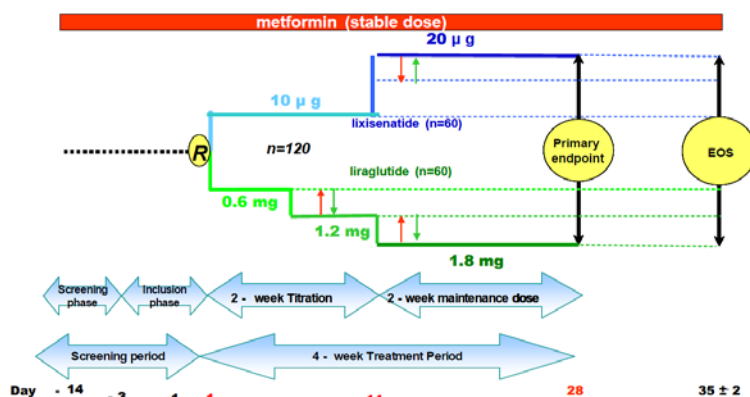


Figure 10 Lixisenatide vs. Liraglutide study design

The primary pharmacodynamic variable examined in this study was the change in $GLU-AUC_{0:30-4:30}$ i.e., the change from baseline in the area under the plasma glucose concentration-time curve calculated using the linear trapezoidal rule, determined from glucose assessments from the time of standardized breakfast start (30 minutes after study medication injection) on Day 28 to 4 hours after injection, relative to the pre-meal glucose concentration.

The change relative to baseline was determined as:

$$\text{Change in } GLU-AUC_{0:30-4:30h} = GLU-AUC_{0:30-4:30h} \text{ on Day 28} - GLU-AUC_{0:30-4:30h} \text{ on Day -1}$$

Secondary pharmacodynamic parameters estimated in the study were:

- To assess the effects of lixisenatide as compared to liraglutide after a 4-week treatment period in patients with type 2 diabetes:
 - on the maximum PPG excursion, and on the changes in insulin, pro-insulin, C-peptide, and glucagon plasma concentrations following a standardized breakfast
 - on the 24-hour profile of plasma glucose
 - on HbA_{1c}
 - on satiety markers (obestatin, PYY3-36 and oxyntomodulin)
- To assess the clinical and laboratory safety profile of lixisenatide and liraglutide over a 4-week treatment period in patients with type 2 diabetes

Plasma Glucose between 0:30-4:30h

Lixisenatide reduced the corrected mean change in plasma glucose $AUC_{0:30-4:30h}$ ($h \cdot mg/dL$) from baseline: -227.25 for lixisenatide compared to -72.83 for liraglutide. The estimated mean treatment difference between lixisenatide and liraglutide treatments was -154.42 [95% CI: -180.30 to -128.54] and was statistically significant ($p < 0.0001$)

Change from baseline in postprandial plasma glucose excursion from T0.30h to T4.30h on Day 28

PPG excursion from the baseline value at Day 28 was -70.43 mg/dL in the lixisenatide group compared to -24.93 mg/dL in the liraglutide group, with a mean treatment difference estimate of -45.50 [95% CI: -55.21 to -35.80] for lixisenatide compared to liraglutide. This difference was statistically significant ($p < 0.0001$).

Plasma glucose concentration over 24 hours on Day 28 and Day -1

Results showed that for all time points between T0.5h to T4:30h, lixisenatide reduced the increase in plasma glucose after a standardized breakfast to a greater extent than liraglutide. However, after T4h30, glucose levels were lower for liraglutide than for lixisenatide at all time points ([Figure 11](#)). This pharmacodynamic observation correlates with the pharmacokinetic characteristics of the two drugs: lixisenatide has a t_{max} between 1 to 3.5 hours in patients with T2DM, while liraglutide has a t_{max} between 8-12 hours¹ post-dosing, therefore it is expected that lixisenatide would exert its action early compared to liraglutide.

¹ Victoza product monograph, accessed at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s0201bl.pdf

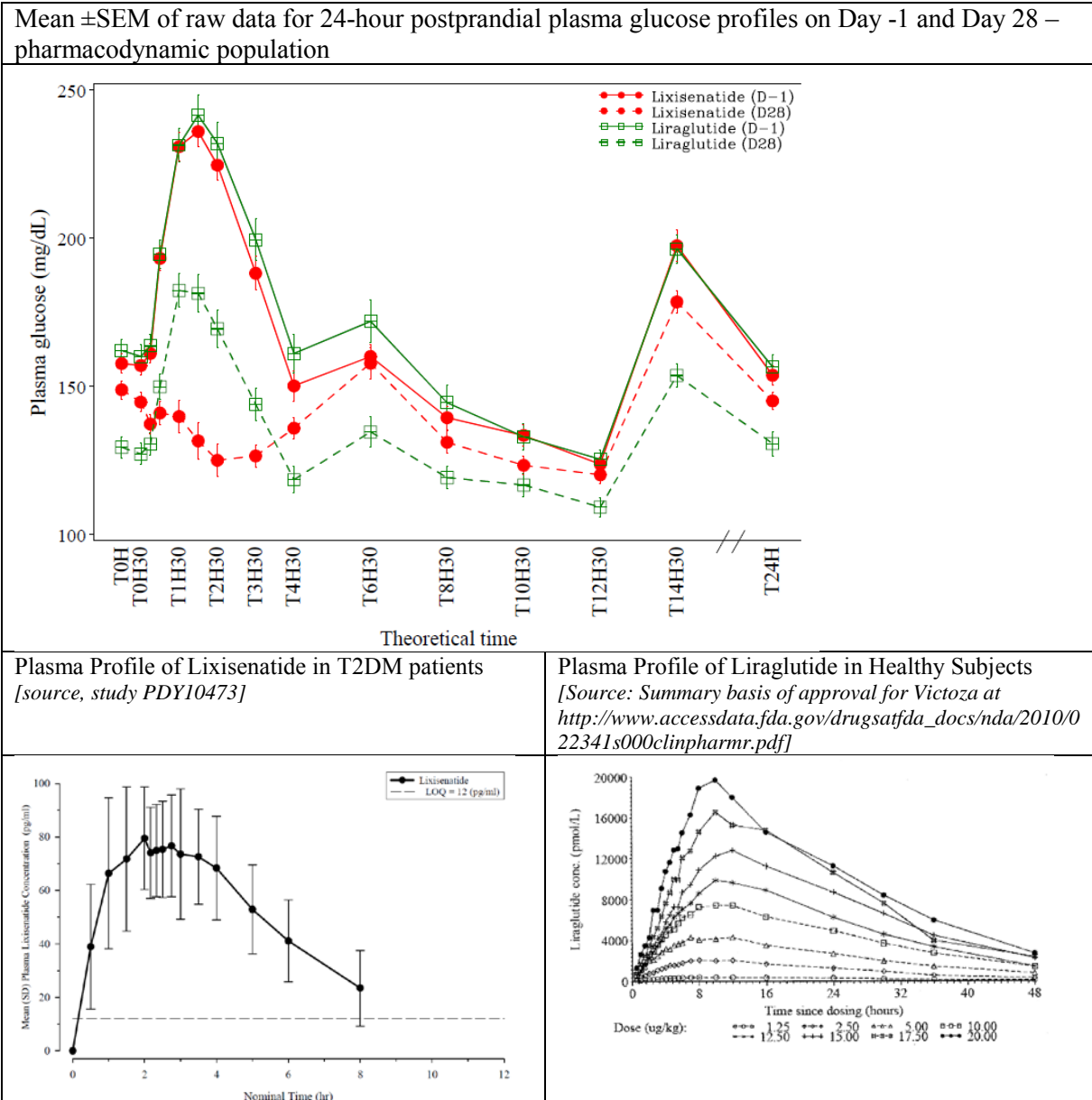
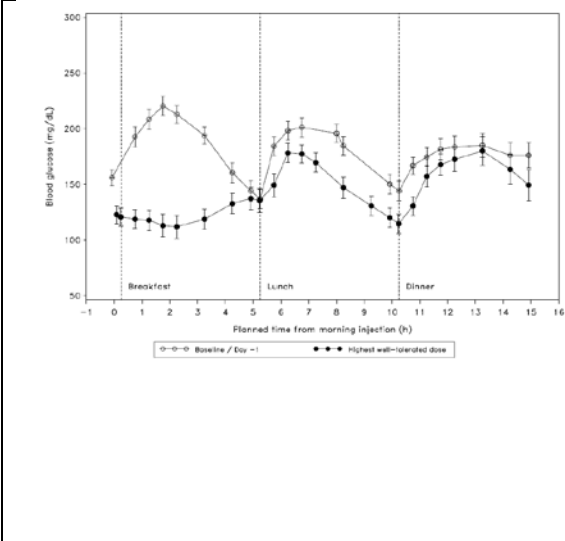


Figure 11 Mean ($\pm$ SEM) plot of 24-hour postprandial plasma glucose profiles on Day -1 and Day 28 – pharmacodynamic population and Comparative plasma profiles of lixisenatide and liraglutide.

A comparison of the blood glucose lowering effect of lixisenatide and liraglutide showed that though lixisenatide lowered blood glucose to a greater extent than liraglutide between the interval of 0-5 hours (between breakfast and lunch), liraglutide had a greater glucose lowering effect compared to lixisenatide between the intervals of 5 – 16 hours post-breakfast for which comparison plots are available ([Figure 12](#)).

Mean $\pm$ SE blood glucose values in the lixisenatide QD group at baseline and at the highest well-tolerated dose (mITT population)
 [source; study ACT6011]



Mean 24-hour profile for plasma glucose for liraglutide
 [Source: page 28, summary basis of approval, accessed at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000clinpharmr.pdf]

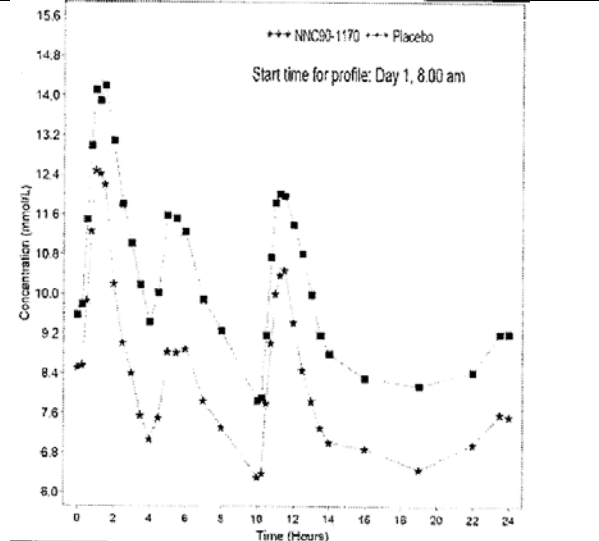


Figure 12 Mean blood glucose values for lixisenatide QD (0-16 hours) and liraglutide (0-24 hours) at baseline.

Reviewer's comment

Based on results of this study, sponsor proposed the following language in their label:



(b) (4)

However, this language is not acceptable

(b) (4)

(b) (4)

2.3.4 Is major route of elimination in humans identified?

In human liver microsomes, lixisenatide showed no significant inhibition of the CYP isozymes

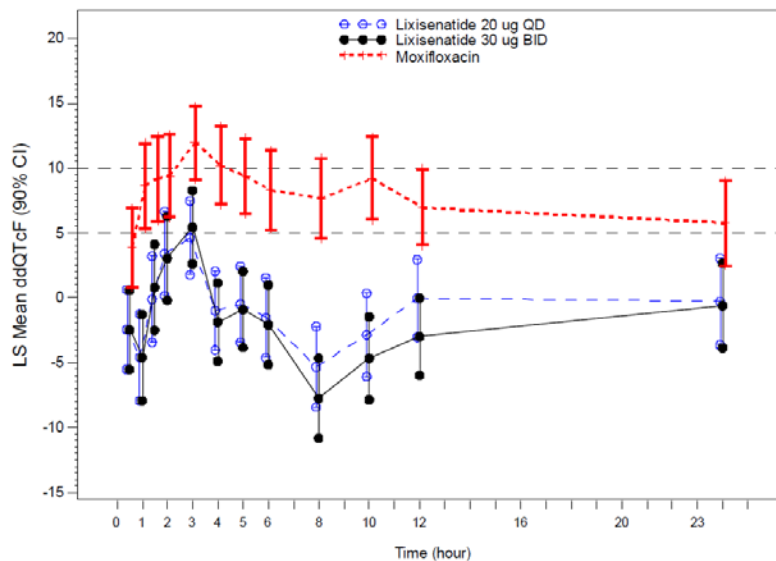
tested (1A2, 2C8, 2C9, 2C19, 2D6, 3A), for which IC_{50} values were all above 20 $\mu\text{mol/L}$ (studies (F2005KIN0088, GMPK-KW 2008-0035). Lixisenatide is a peptide consisting of 44 amino acids, and is subject to standard proteolytic processes that result in degradation to small peptides and amino acids. The *in vitro* metabolism of lixisenatide in human plasma was very slow, with a mean apparent terminal elimination half-life ($t_{1/2}$) of approximately 35 hours. Lixisenatide was intensively metabolized in the kidney and liver S9 fractions. In humans, the percentage of lixisenatide remaining in the S9 liver and kidney fractions after 60 minutes was 8% and 11% respectively (study F2006KIN0001). Overall, 28 metabolites were detected after incubation of lixisenatide in human liver and kidney S9 fractions. All metabolites were degraded peptide products of lixisenatide. Peptides (mean molecular weight <50 KD) are assumed to be eliminated through renal filtration followed by tubular reabsorption and subsequent metabolic degradation.

2.3.5 Does this drug prolong the QT or QTc Interval?

A formal consult to review the thorough QT study was submitted to the IRT. Based on the IRT review the following observations were made:

The largest upper bounds of the 2-sided 90% CI for the mean difference between lixisenatide (20 μg q.d. and 30 μg b.i.d.) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was higher than 5 ms, and the moxifloxacin profile over time is demonstrated in [Figure 13](#), indicating that assay sensitivity was established.

In this randomized, double-blind, double-dummy, multiple dose, placebo-controlled parallel study, 91 healthy subjects received lixisenatide 20 μg once daily, lixisenatide 30 μg twice daily, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in [Table 21](#).



(Note: CIs are all unadjusted including moxifloxacin)

Figure 13 Mean and 90% CI $\Delta\Delta\text{QTcF}$ Timecourse

[Source: Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review, Figure 3, Page 19]

Table 21 Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Lixisenatide (20 µg and 30 µg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Lixisenatide 20 µg q.d.	3	4.6	(1.8, 7.5)
Lixisenatide 30 µg b.i.d.	3	5.5	(2.6, 8.3)
Moxifloxacin 400 mg*	3	12.0	(8.5, 15.4)

* Multiple endpoint adjustment of 3 time points was applied.

[Source: Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review, Table 1, Page 2]

The selection of 20-µg q.d. dose as the therapeutic dose for TQT study is reasonable. The supra-therapeutic dose (30 µg b.i.d.) represents the highest dose tested. The overall exposure as well as the variability of the pharmacokinetic parameters increased largely in the antibody-positive subjects. The pharmacokinetic data in this study covered a wide range of lixisenatide exposure with mean values of C_{max} up to 209 pg/mL and AUClast up to 979 pg·h/mL in antibody-negative subjects, and C_{max} up to 945 pg/mL and AUClast up to 12500 pg·h/mL in antibody-positive subjects. The mean C_{max} and AUC of lixisenatide was approximately 40% higher at 30 µg b.i.d. than at 20 µg q.d. in antibody-negative subjects or antibody-positive subjects.

The relationship between $\Delta\Delta\text{QTcF}$ and lixisenatide concentrations is visualized in [Figure 14](#). Based on visual diagnostics, the exposure-response relationship can be described better with a log-linear model compared to that with a linear model. As shown in [Figure 14](#), the slope of $\Delta\Delta\text{QTcF}$ versus log lixisenatide concentration is positive and significant (slope 1.5266 with p-value <.0001 for a log-linear mixed effect model including intercept).

However, there is no substantial QT prolongation in the exposure range at the therapeutic dose of 20 µg q.d. and the supra-therapeutic dose of 30 µg b.i.d. ([Figure 14](#), bottom right panel).

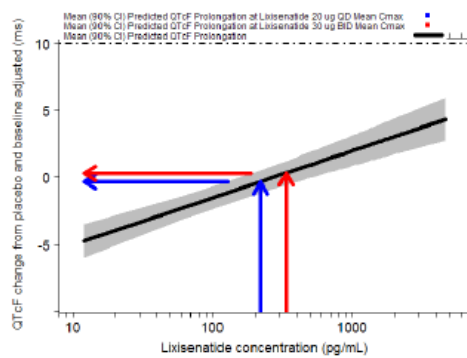
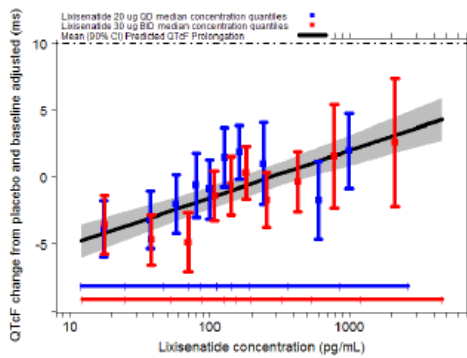
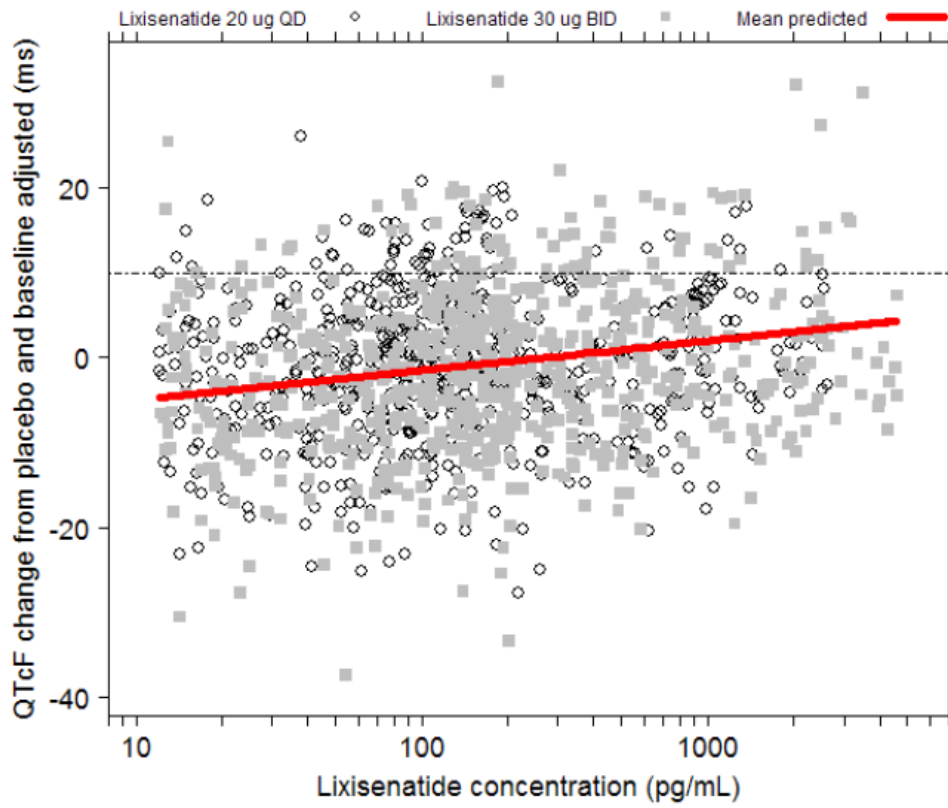


Figure 14 $\Delta\Delta$ QTcF vs. Lixisenatide Concentration

[Source: Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review, Figure 4, Page 27]

2.3.6 Does the dose-response relationship for efficacy support the proposed dose and dosing regimen of 20 µg once daily?

Yes, the dose-response relationship of efficacy along with the dose-response relationship of safety (discussed later) supports the proposed dosing regimen of 20 µg once daily.

The sponsor studied only one dose of 20 µg QD in all the Phase 3 trials. All the trough concentrations data in the Phase 3 trials were below the limit of quantification. Thus, dose/exposure response relationship for safety and efficacy is limited to data available from a single Phase 2 trial of 13-week duration (Study #DRI6012).

The selection of 20 µg QD dose in all the Phase 3 trials, was primarily based on a Phase 2 dose ranging study of 13-week treatment duration (Study #DRI6012). In this Phase 2 study, subjects were randomized to receive 5 µg, 10 µg, 20 µg, and 30 µg of lixisenatide dose as QD and BID dosing regimen. The primary efficacy endpoint for this Phase 2 study was change from baseline in HbA_{1c} at week 13. As shown in [Figure 15](#), a clear dose response relationship was observed, where increasing doses within the QD and BID-dosing regimen resulted in increase in response in terms of HbA_{1c}. Compared to proposed 20 µg QD dosing, 10 µg BID-dosing regimen showed slight numerically greater reduction in HbA_{1c} (-0.69 with 20 µg QD vs. -0.78 with 10 µg BID-dosing). Furthermore, [Figure 16](#) shows cumulative distribution function (CDF) plots for change from baseline HbA_{1c} between these two dosing regimens. Overlapping CDF plots between 20 µg QD and 10 µg BID dosing indicates that the distribution for change from base line in HbA_{1c} is similar across both the dosing group ([Figure 16](#)).

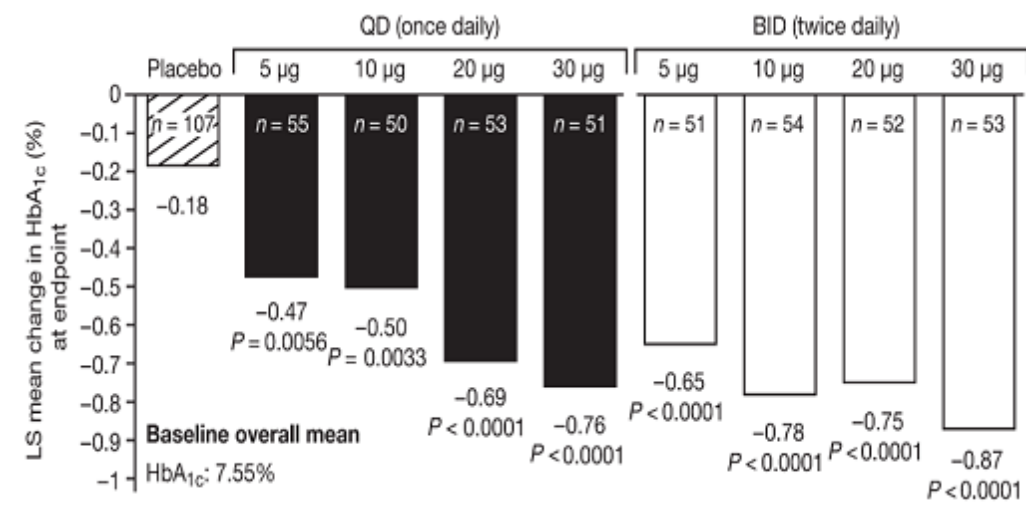


Figure 15 Mean change in HbA_{1c} at endpoint (ITT population) (Study DRI6012)

BID = twice daily; HbA_{1c} = glycosylated hemoglobin; ITT = intent-to-treat; LS = least square; n = number of patients; QD = once daily

[Source: Sponsor's Summary of Clinical Efficacy report Pg 131]

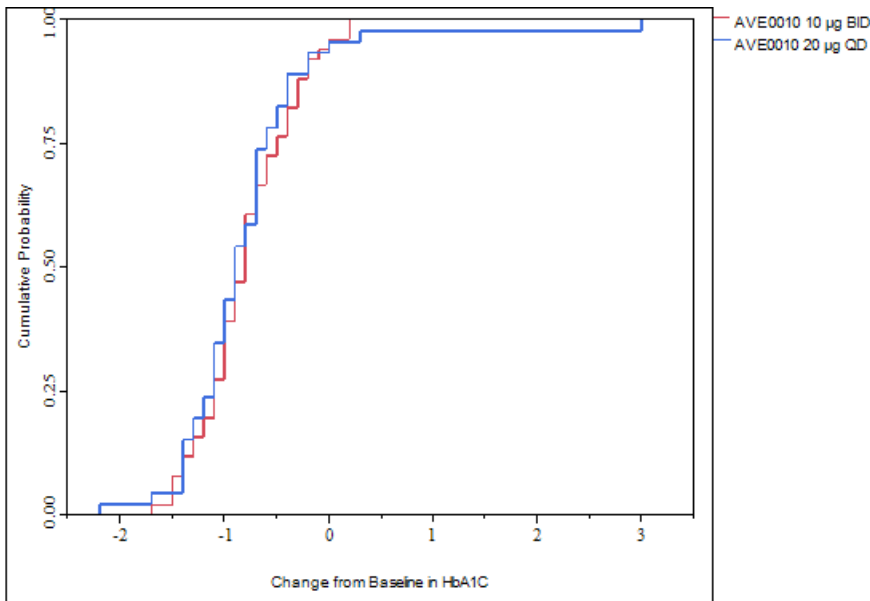


Figure 16 Cumulative distribution function plot for mean change from baseline in HbA_{1c} at week 13 (Study DRI6012).

AVE0010 10 µg BID = Lixisenatide 10 µg BID dosing; AVE0010 20 µg QD = Lixisenatide 20 µg QD dosing

[Figure 17](#), represents the dose-response relationship for secondary pharmacodynamic endpoints: A) fasting plasma glucose (FPG) and B) 2-hr post prandial glucose (PPG) at week 13. A clear dose response relationship was observed for both secondary endpoints, where increasing doses within the QD and BID-dosing regimen resulted in increase in response. Compared to proposed 20 µg QD dosing, 10 µg BID-dosing regimen showed numerically greater reduction in FPG whereas for PPG 20 µg QD dosing seems to be numerically better than 10 µg BID dosing. Lixisenatide has a short plasma half-life of around 2-4 hours. Thus, better control of FPG with BID dosing of lixisenatide is expected since BID dosing can provide glucose control at both morning and evening meal and hence that could result in better FPG with BID dosing. In addition, better effect on PPG with 20 µg QD dose is expected since with QD dosing 20 µg of dose is given at once before meal and hence more effect on PPG as compared to BID dosing where the 20 µg dose is divided into morning and evening dose of 10 µg.

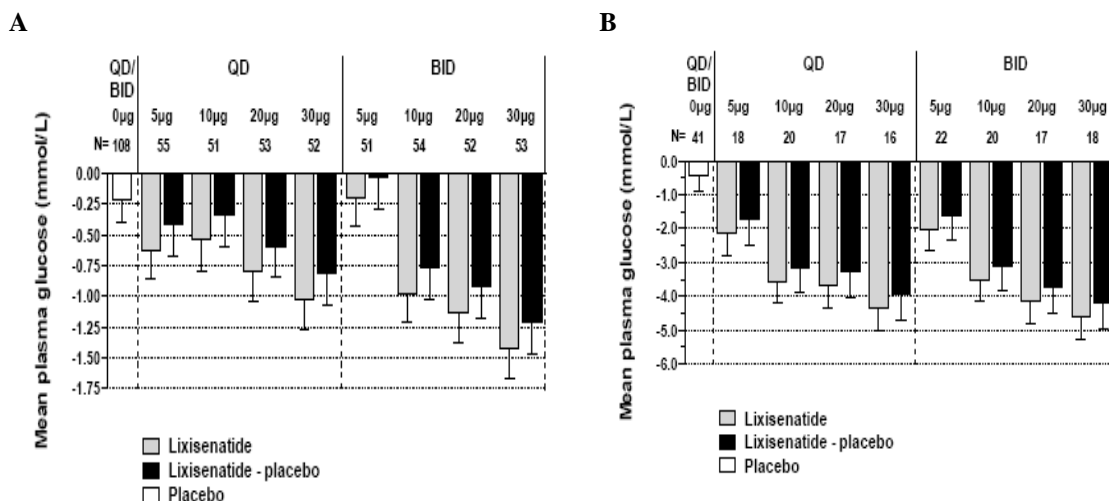


Figure 17 Mean change from baseline in A) fasting plasma glucose B) 2 hour post prandial glucose (Study DRI6012)

BID = twice daily; *n* = number of patients; QD = once daily [Source: Sponsor's Summary of Clinical Pharmacology report Pg 118]

Dose-Response relationship for Weight Loss: A clear dose-response relationship for weight loss was observed for each dosing regimen, i.e., the higher the lixisenatide dose within a regimen (QD or BID) the larger the mean decrease in body weight. [Figure 18](#) shows the mean ($\pm$ SE) change in body weight by time and by treatment group. The data for mean change in weight (kg) from baseline to endpoint (week 13) is presented in [Table 22](#). Compared to 10 µg BID dose, 20 µg QD dose have a greater weight loss change.

Table 22 Mean change in weight (kg) from baseline to endpoint – ITT population in Phase 2 Trial (Study#DRI6012)

	QD Dosing					BID Dosing			
	Placebo (n=108)	5 µg (n=55)	10 µg (n=51)	20 µg (n=53)	30 µg (n=52)	5 µg (n=51)	10 µg (n=54)	20 µg (n=52)	30 µg (n=53)
Baseline Mean (SD) Weight (kg)	87.66 (13.69)	84.83 (15.56)	90.66 (17.37)	88.93 (17.11)	87.17 (15.19)	86.26 (14.41)	90.02 (16.90)	88.18 (16.76)	87.55 (13.74)
Change from Baseline Mean (SD) Weight (kg)	-1.51 (2.22)	-1.51 (2.65)	-2.02 (2.64)	-2.59 (3.14)	-3.02 (2.86)	-1.65 (2.56)	-1.85 (2.74)	-2.18 (2.15)	-3.43 (2.68)

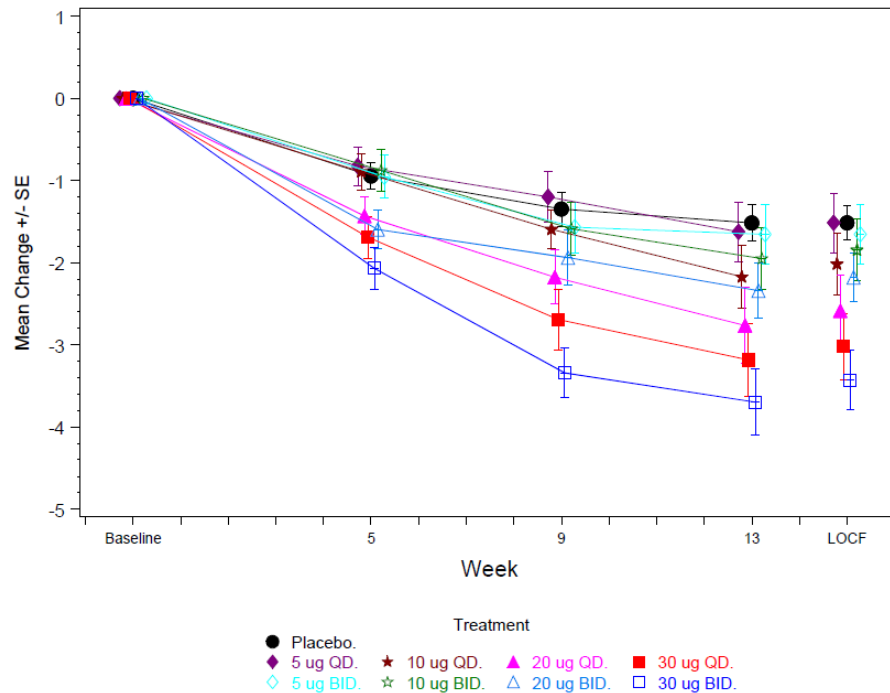


Figure 18 Mean ($\pm$ SE) Change in Weight (kg) by Visit and at Endpoint – ITT Population

BID = twice daily; QD = once daily

[Source: Sponsor's Study report for DRI6012 Pg 88]

2.3.7 Does the dose-response relationship for safety support the proposed dose and dosing regimen of 20 μ g once daily?

Yes, the dose-response relationship of safety supports the proposed dosing regimen of 20 μ g once daily.

Gastrointestinal Disorder: The major safety issues associated with lixisenatide were gastrointestinal disorders such as nausea and vomiting. The trough concentrations data in the Phase 3 trials were below the limit of quantification. In addition sponsor studied only one dose in all the Phase 3 trials. Thus, dose/exposure response relationship for safety is limited to data available from a single Phase 2 trial of 13-week duration (Study #DRI6012). In the Phase 2 study, a clear dose-response relationship within both regimens was seen in the number of subjects with GI related adverse events. The frequencies for GI side effects ranged from 21.8 % (5 μ g) to 51.9 % (30 μ g) in lixisenatide QD groups and from 22.6% (5 μ g) to 57.4 % (30 μ g) in lixisenatide BID groups. Doses higher than 20 μ g in both QD and BID dosing regimen resulted in more gastrointestinal related adverse events ([Table 23](#)).

Table 23 Dose-response relationship for GI disorders in Phase 2 Trial (Study#DRI6012)

	QD Dosing					BID Dosing			
	Placebo (109)	5 µg (55)	10 µg (52)	20 µg (55)	30 µg (54)	5 µg (53)	10 µg (56)	20 µg (54)	30 µg (54)
Subjects with any TEAEs (% of Subjects)	65 (29%)	31 (56.4%)	26 (50%)	37 (67.3%)	42 (77.8%)	30 (56.6%)	32 (57.1%)	38 (70.4%)	40 (74.1%)
Gastrointestinal Disorders (% of Subjects)	21 (19%)	12 (21.8%)	11 (21.2%)	23 (41.8%)	28 (51.9%)	12 (22.6%)	15 (26.8%)	25 (46.3%)	31 (57.4%)

Effect on Heart Rate: Lixisenatide was not found to affect the heart rate. No difference in heart rate was observed between 20 µg QD dose and 10 µg BID dose. Also, in through QT study no difference in heart rate was observed following 20 µg QD dose and 30 µg BID dose. Please refer to Pharmacometrics review and QT-IRT review dated 06/06/12 under IND62724 for further details.

2.3.8 Does the benefit risk analysis support the proposed 20 µg QD dosing over 10 µg BID dosing?

Yes, the benefit risk analysis of efficacy and safety supports the proposed dosing regimen of 20 µg once daily due to the following reasons:

Efficacy

- In the dose ranging Phase 2 study, a clear dose response relationship was observed, where increasing doses from 5 µg to 30 µg, within the QD and BID-dosing regimen resulted in increase in response in terms of HbA_{1c} (Figure 15).
- Compared to proposed 20 µg QD dosing, 10 µg BID-dosing regimen showed numerically slightly higher reduction in HbA_{1c}. However, the added benefit with 10 µg BID-dosing should be weighed against narrow time window left for the administration of concomitant medication because of the effect of lixisenatide on delaying gastric emptying time. Furthermore, Figure 16 shows that cumulative distribution plots for change from baseline HbA_{1c} is highly overlapped between the these two dosing regimens.
- Compared to 10 µg BID dose, 20 µg QD dose showed a numerically greater weight loss change.

Safety

- In the dose ranging Phase 2 study, doses higher than 20 µg in both QD and BID dosing regimen resulted in more gastrointestinal related adverse events (Table 23).
- Additionally, compared to 20 µg QD dosing regimen 10 µg BID dosing regimen had less gastrointestinal related side effects. However, as stated above, the added safety benefit with BID dosing regimen needs to be counterbalanced with the inconvenience of co-administration of other drugs.

Practicality

- Lixisenatide delays the gastric emptying time and hence concomitant medications need to be administered ^{(b) (4)} 1 hour before lixisenatide administration or with next meal for those drugs that have to be administered with food.
- Thus, with BID dosing regimen the subjects will have narrow window for taking concomitant medications and hence we agree with the sponsor's proposed 20 µg QD dosing regimen as acceptable from a practical standpoint.

2.3.9 Does the efficacy and safety data support the proposed one-step dosing regimen of 10 µg once daily for 14 days followed by 20 µg once daily?

Yes, sponsor has proposed 1-step dosing recommendation of starting dose of 10 µg QD for 14 days followed by maintenance dose of 20 µg QD, which is acceptable from efficacy and safety standpoint.

In majority of the Phase 3 trials, the sponsor used a 2-step dosing regimen. In the 2-step dosing the patients were started with the initiation dose of 10 µg QD lixisenatide for 1 week followed by 15 µg QD for 1 week, and subsequently 20 µg QD as a maintenance dose. Later in the development phase sponsor used a 1-step dosing regimen, which is also the current proposed dosing recommendation in the product label. In the 1-step dosing regimen, patients were given 10 µg dose for 2 weeks followed by 20 µg QD maintenance dose. To evaluate the impact of 1-step vs. 2-step dose increase on efficacy and safety sponsor conducted two Phase 3 trials.

Effect of 1-Step vs 2-Step Dose Increase on Efficacy

Sponsor's analysis of the 1-step and 2-step dose initiation in two Phase 3 studies, EFC6018 and EFC10743 is shown in [Figure 19](#). Sponsor showed that a significant HbA1c reduction from baseline of similar magnitude with both dose increase regimens (-0.85% for the 1-step group and -0.73% for the 2-step group in Study EFC6018; -0.83% for the 2-step group and -0.92% for the 1-step group in Study EFC10743). Thus, based on sponsor's analysis, the 1-step and 2-step dose initiation regimens were similar in terms of efficacy. Such similar results were expected since the only difference between the two groups was a higher dose (15 µg compared with 10 µg) during the second week of treatment.

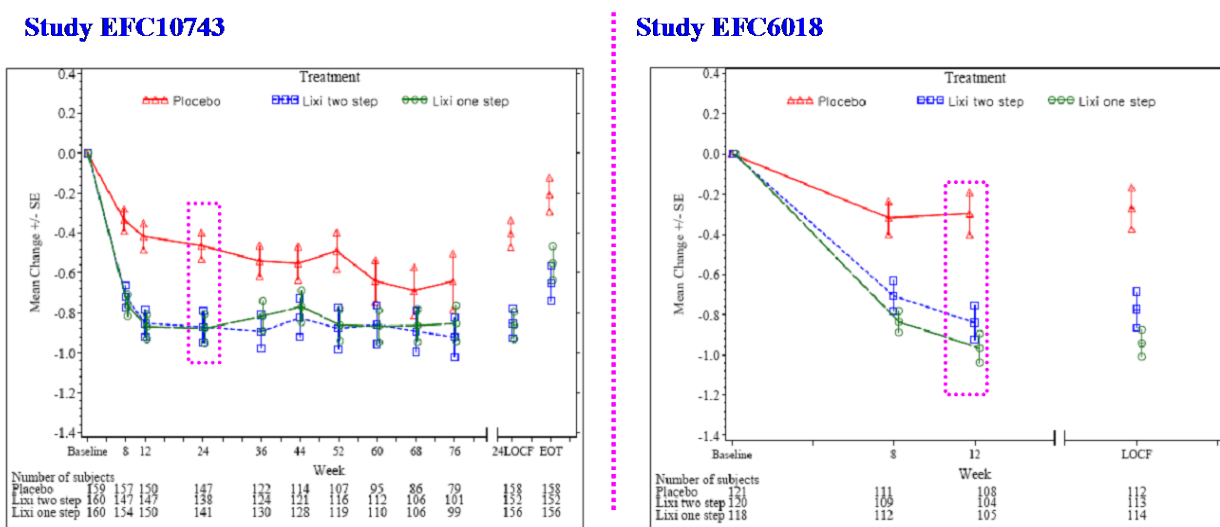


Figure 19 Time-profiles for adjusted mean change from baseline in HbA1c in Phase 3 trials EFC10743 (left) and EFC60182 (right) upon administration as placebo (red), lixisenatide 20 µg QD dose administered as one step (green), and 20 µg QD dose administered as two steps (blue)

[Source: Sponsor's Summary of Clinical Efficacy report Pg 149]

Effect of 1-Step vs 2-Step Dose Increase on Safety

Survival plot for comparing time to GI event in two Phase 3 trials showed no difference in GI related adverse events in both the dosing regimen ([Figure 20](#)). We evaluated time to gastrointestinal adverse events in both 1-step and 2-step dosing regimen. As it is known that, the only difference in

1-step vs 2-step dosing regimen is a higher dose 15 µg (compared with 10 µg in 1-step) during the second week of treatment. After second week of the treatment, both the dose groups have same maintenance dose of 20 µg QD. Survival plot for comparing time to GI event in two Phase 3 trials showed no significant differences in GI related adverse events in both the dosing regimen (Figure 20).

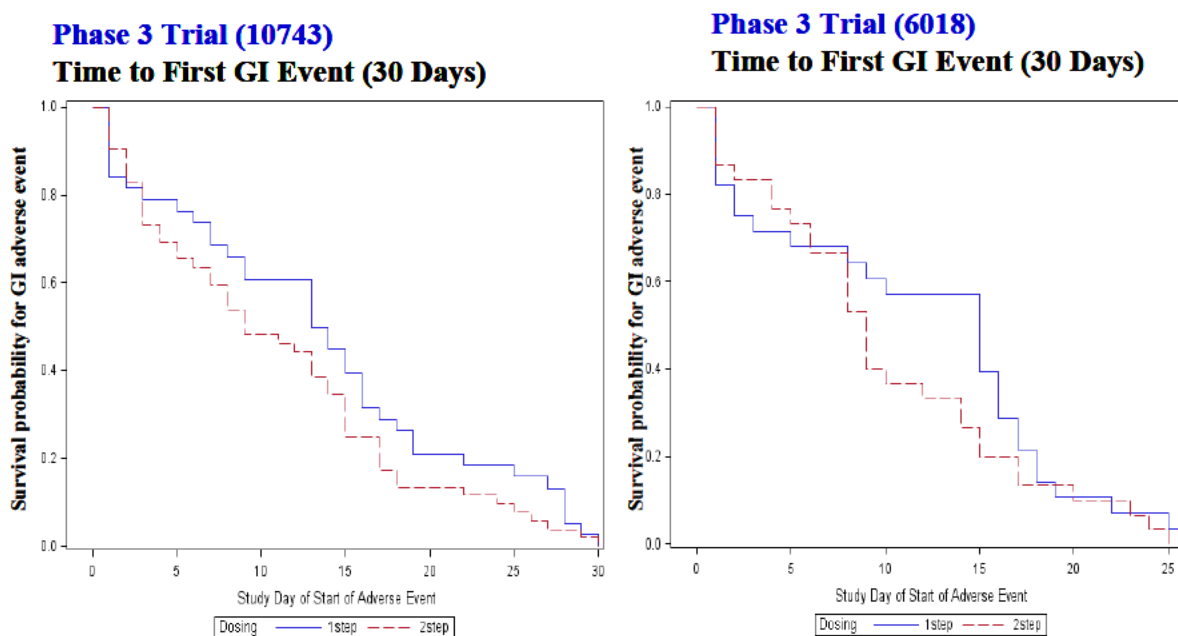


Figure 20 Survival plot for time to GI event in first 30 days of the treatment in Phase 3 trials EFC10743 (left) and EFC60182 (right). Lixisenatide 20 µg QD dose administered as one step (blue), and 20 µg QD dose administered as two steps (red).

2.3.10 *What is the impact of Anti-drug antibody on efficacy? - Is it possible to identify the patient population early on that are likely to be non-responders?*

- Higher antibody concentrations resulted in attenuated HbA_{1c} response. Antibody concentration response analysis showed a lower change from baseline in HbA_{1c} with increasing antibody concentrations based on week 4 and week 24 antibody concentrations.
- No correlation was observed between week 4 and week 24 antibody data. Since the week 4 antibody data is not predictive of week 24 antibody data, the analysis of antibody concentration to efficacy is exploratory in nature and cannot identify non responders early on with the drug treatment. Please see Pharmacometrics review in section 4.3 for further details.

2.3.11 *What are the characteristics of the exposure-calcitonin relationships (dose-response, concentration-response) with regards to thyroid safety?*

Calcitonin data were collected in all Phase 3 studies that lasted over 12 weeks in duration. The sponsor implemented calcitonin monitoring via a protocol amendment when most of the Phase 3 studies were already ongoing, therefore baseline values for most of the patients were not collected.

In the Phase 3 placebo-controlled studies, 33 patients (1.4%) in the lixisenatide group and 21 patients (1.6%) in the placebo group reported abnormal calcitonin on-treatment values in the range

≥ 20 pg/mL to 50 pg/mL during the entire treatment period ([Table 24](#)). One lixisenatide treated patient (Patient No. 276501006 in Study EFC6015) with a maximum on-treatment calcitonin value in the range of ≥ 20 pg/mL to 50 pg/mL had already reported an abnormal calcitonin value of 23.9 pg/mL at baseline, and was subsequently diagnosed with thyroid C-cell hyperplasia on Day 1. After 63 days of treatment, this patient discontinued study treatment.

Ten patients (0.4%) in the lixisenatide group and 2 patients (0.1%) in the placebo group reported values ≥ 50 pg/mL in Phase 3 placebo-controlled studies, but for the majority of the patients the baseline calcitonin values were not available (Table 24). One of the placebo patients with calcitonin ≥ 50 pg/mL (Patient No. 276302003 in Study EFC10743) was diagnosed with medullary thyroid cancer. Furthermore, 7 (0.2%) lixisenatide patients and 3 (0.2%) placebo patients with a calcitonin on-treatment value ≥ 20 pg/mL discontinued study treatment due to a treatment emergent adverse event (TEAE) of blood calcitonin increased. Lixisenatide group did not have any serious cases. One lixisenatide patient (Patient No. 642302022 in Study EFC10743) had an on-treatment potentially clinically significant abnormality (PCSA) calcitonin value who reported a serious TEAE of “blood calcitonin increased” (mild) but did not discontinue from treatment.

No additional patient reported a calcitonin value ≥ 50 pg/mL during the post-treatment period.

Table 24 Serum calcitonin: Number (%) of patients with abnormalities (PCSA) in Phase 3 placebo-controlled studies: entire treatment period - safety population

Laboratory criteria		
Baseline status	Placebo	Lixisenatide
Post-baseline	(N=1517)	(N=2630)
Calcitonin (pg/mL)		
Total*		
≤ULN	1273/1411 (90.2%)	2108/2375 (88.8%)
>ULN - <20 pg/mL	115/1411 (8.2%)	224/2375 (9.4%)
≥20 pg/mL - <50 pg/mL	21/1411 (1.5%)	33/2375 (1.4%)
≥50 pg/mL	2/1411 (0.1%)	10/2375 (0.4%)
Missing		
≤ULN	644/726 (88.7%)	1355/1539 (88.0%)
>ULN - <20 pg/mL	70/726 (9.6%)	157/1539 (10.2%)
≥20 pg/mL - <50 pg/mL	11/726 (1.5%)	20/1539 (1.3%)
≥50 pg/mL	1/726 (0.1%)	7/1539 (0.5%)
≤ULN		
≤ULN	622/643 (96.7%)	748/778 (96.1%)
>ULN - <20 pg/mL	21/643 (3.3%)	28/778 (3.6%)
≥20 pg/mL - <50 pg/mL	0/643	1/778 (0.1%)
≥50 pg/mL	0/643	1/778 (0.1%)
>ULN - <20 pg/mL		
≤ULN	6/34 (17.6%)	5/50 (10.0%)
>ULN - <20 pg/mL	22/34 (64.7%)	39/50 (78.0%)
≥20 pg/mL - <50 pg/mL	6/34 (17.6%)	6/50 (12.0%)
≥50 pg/mL	0/34	0/50
≥20 pg/mL - <50 pg/mL		
≤ULN	1/8 (12.5%)	0/7
>ULN - <20 pg/mL	2/8 (25.0%)	0/7
≥20 pg/mL - <50 pg/mL	4/8 (50.0%)	6/7 (85.7%)
≥50 pg/mL	1/8 (12.5%)	1/7 (14.3%)
Laboratory criteria		
Baseline status	Placebo	Lixisenatide
Post-baseline	(N=1517)	(N=2630)
≥50 pg/mL		
≤ULN	0/0	0/1
>ULN - <20 pg/mL	0/0	0/1
≥20 pg/mL - <50 pg/mL	0/0	0/1
≥50 pg/mL	0/0	1/1 (100%)

Studies included: EFC6014, EFC6015, EFC6016, EFC10743, EFC6017, EFC10781, EFC11321 and EFC10887. Data were not collected in EFC6018.

PCSA: Potentially clinically significant abnormalities.

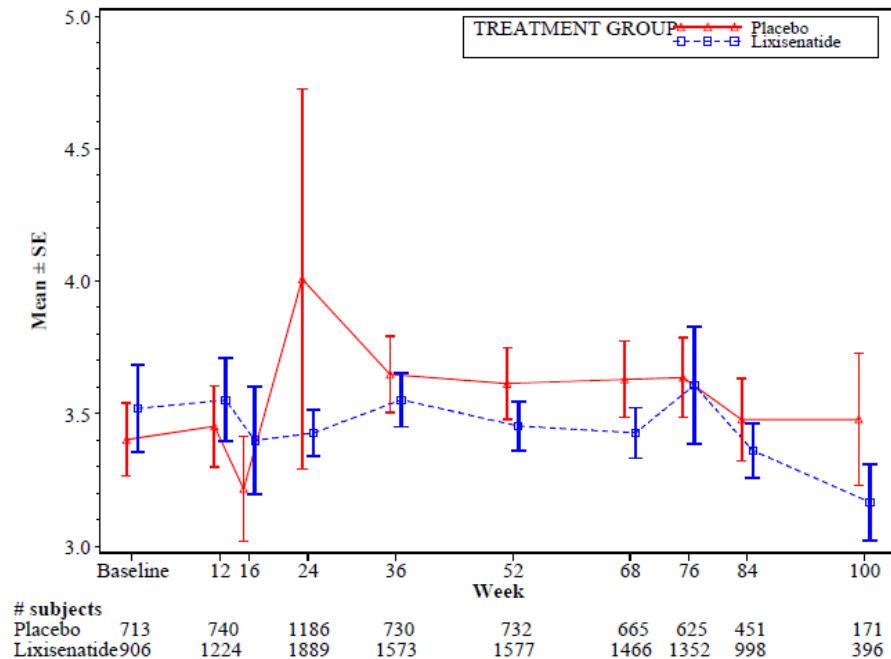
*Regardless of baseline.

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once. The denominator (N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline by baseline PCSA status. Only the worst case for each patient is presented by baseline status.

[Source: Sponsor's Table 43 Page 186, Report 2.7.4 Summary of Clinical Safety]

In the Phase 3 placebo-controlled studies, mean calcitonin values at baseline were 3.52 pg/mL in the lixisenatide group and 3.40 pg/mL in the placebo group. During the entire treatment period and compared to baseline values, there were no relevant changes in mean calcitonin values over time in

the lixisenatide group (Figure 21). One patient in the placebo group (diagnosed later on with medullary thyroid C-cell cancer, Patient No. 276302003 in Study EFC10743) presented a high value that triggered a spike in the placebo curve at Week 24. Lixisenatide group remains parallel to the placebo group without any specific signal if this patient was excluded from the calcitonin curve.



Timepoints are presented up to 2 years.
 Studies included: EFC6014, EFC6015, EFC6016, EFC6017, EFC10743, EFC10781, EFC10887 and EFC11321. Data were not collected in EFC6018. Week 16 only includes EFC10781.

Figure 21 Plot of calcitonin by visit for Phase 3 placebo-controlled studies: entire treatment period - safety population

[Source: Sponsor’s Figure 13 Page 188, Report 2.7.4 Summary of Clinical Safety]

The analysis of mean calcitonin values in the Phase 2/3 study pool showed similar results for lixisenatide versus all comparators.

Calcitonin level data were also collected in the 26-week Phase 1 Study TDR11215, a study to evaluate the effect of subcutaneous doses of 20 µg lixisenatide once daily on sperm production. The overall incidence of calcitonin levels >ULN was 3.3% and 4.1% in the placebo and lixisenatide group, respectively. No subject had a calcitonin value of ≥20 pg/mL. Between baseline and the last on-treatment value, calcitonin levels remained stable over time throughout the study in both treatment groups.

2.4 Intrinsic Factors

2.4.1 What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based on population PK analysis age, gender, race and body weight have no clinically meaningful effect on pharmacokinetics of lixisenatide (See Appendix, Pharmacometrics Review)

2.4.1.1 Age

The sponsor conducted a dedicated trial (POP11814) to assess the pharmacokinetics of lixisenatide given as a single 20 µg dose in elderly healthy subjects and matched young healthy subjects.

Results from this trial showed that the mean exposure in elderly subjects was higher than in young healthy subjects (point estimates AUC_{last} 1.26 [90% CI 1.03 to 1.55] and AUC 1.29 [90% CI 1.06 to 1.57]). The $t_{1/2z}$ was prolonged about 1.6 times in elderly subjects as compared to young subjects (point estimates $t_{1/2z}$ 1.57 [90% CI 1.41 to 1.75]) (Table 25). C_{max} and t_{max} were comparable in both groups.

Table 25 Estimates of age ratios of lixisenatide elderly versus young subject with 90% confidence interval

Parameter	Comparison	Estimate	90% CI
C_{max}	Elderly/young	0.94	(0.81 to 1.09)
AUC_{last}	Elderly/young	1.26	(1.03 to 1.55)
AUC	Elderly/young	1.29	(1.06 to 1.57)
$t_{1/2z}$	Elderly/young	1.57	(1.41 to 1.75)

[Source: Sponsor's Table 15 Page 57, Report POP11814]

As the elderly subjects generally had lower CL_{CR} rates than the young subjects (elderly: 9 out of 18 subjects had CL_{CR} values of 50 to 80 mL/min, the remaining 9 subjects had CL_{CR} values of >80 mL/min; young: all 18 subjects had CL_{CR} values of >80 mL/min), at least part of the increased exposure to lixisenatide in the elderly subjects may be accounted for by the decreased renal CL of lixisenatide in these subjects.

In the population PK analysis, age was not identified as a significant covariate on the apparent clearance of In the population PK analysis of lixisenatide, There is a trend for decrease in clearance with increasing age (Figure 22, panels A and B). Age was found to be highly correlated to cCrCL and thus after inclusion of creatinine clearance in the final model resulted in no systematic trend between inter-individual variability on clearance and age (Figure 22, panel C).

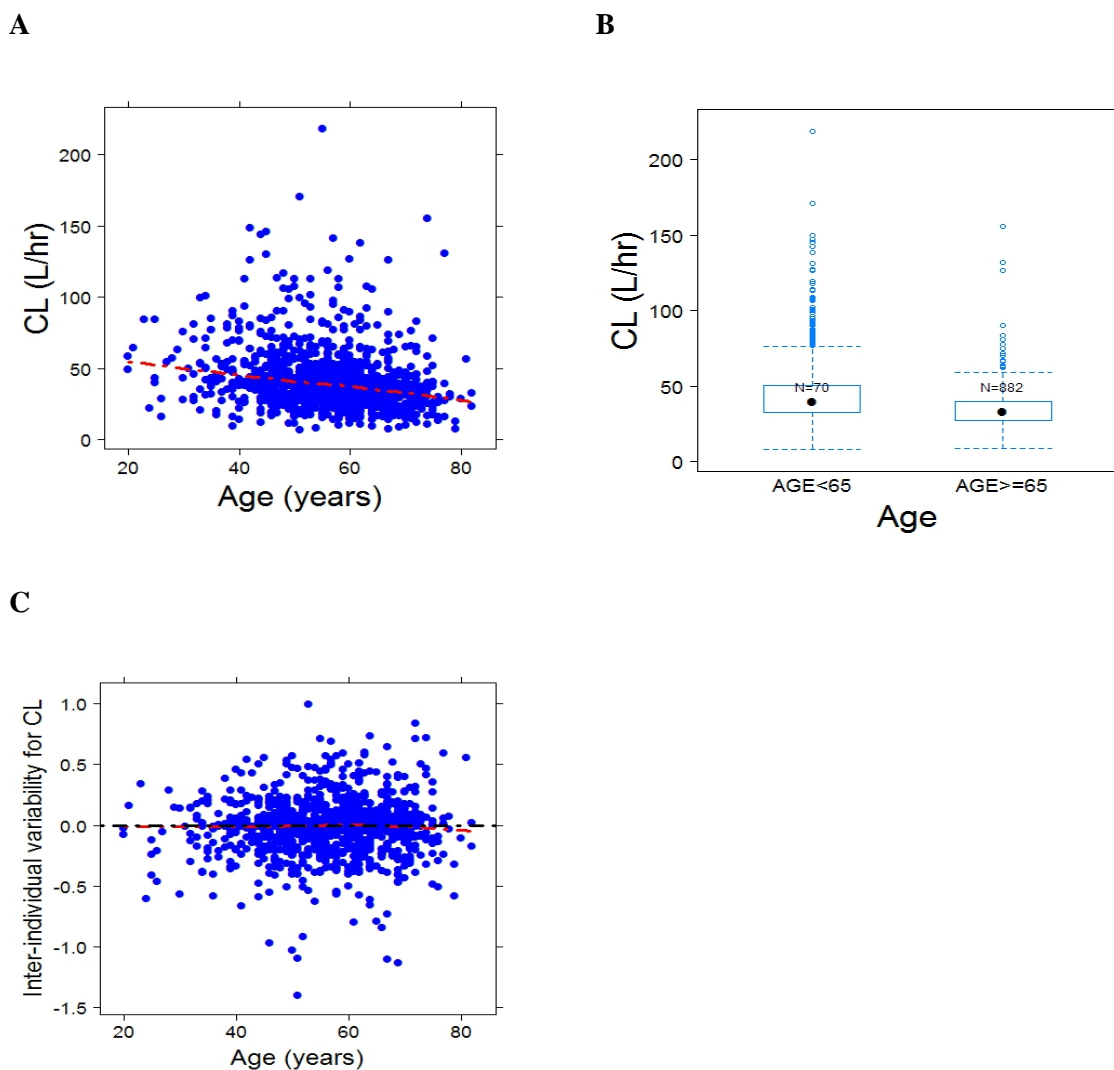


Figure 22 A) Scatter plot for clearance vs. age B) Boxplot of clearance vs. age and C) Inter-individual variability on clearance vs. age

2.4.1.2 Gender and Race

A pooled analysis of healthy subjects participating in Phase 1 studies (studies in which male and female subjects participated, and in which lixisenatide was administered at a dose of 20 μg), showed that a slightly increased exposure to lixisenatide was observed in females, which correlated well with the lower average body weight and smaller volume of distribution in these subjects (Table 26). This tendency was seen for both single and multiple dose data (Table 27). In the antibody-positive subjects, these differences by gender were confounded by the presence of immune complex (e.g., antibody) bound drug, which comprises a sizable fraction of the total circulating drug.

These differences in lixisenatide exposure by gender are most likely related to differences in body weight because the population PK analysis for lixisenatide demonstrated that body weight is one of the covariates for the PK of lixisenatide; no isolated effect of gender was identified. This rationale is supported by data obtained from a Phase 1 study in healthy Chinese subjects (Table 28). In this population, the difference in

body weight between males and females was much less pronounced than in the pooled Phase 1 studies, and thus the difference in exposure to lixisenatide was also much less pronounced.

Any apparent difference between males and females in the exposure to lixisenatide may be due to differences in body weight between the genders rather than the differences between the genders ([Table 28](#)).

In the population PK analysis of lixisenatide based upon data from studies in healthy subjects as well as patients with T2DM, no isolated effect of gender and race was identified. [Figure 23](#) and shows that in the final model the inter-individual variability in clearance cannot be explained by gender and race, respectively.

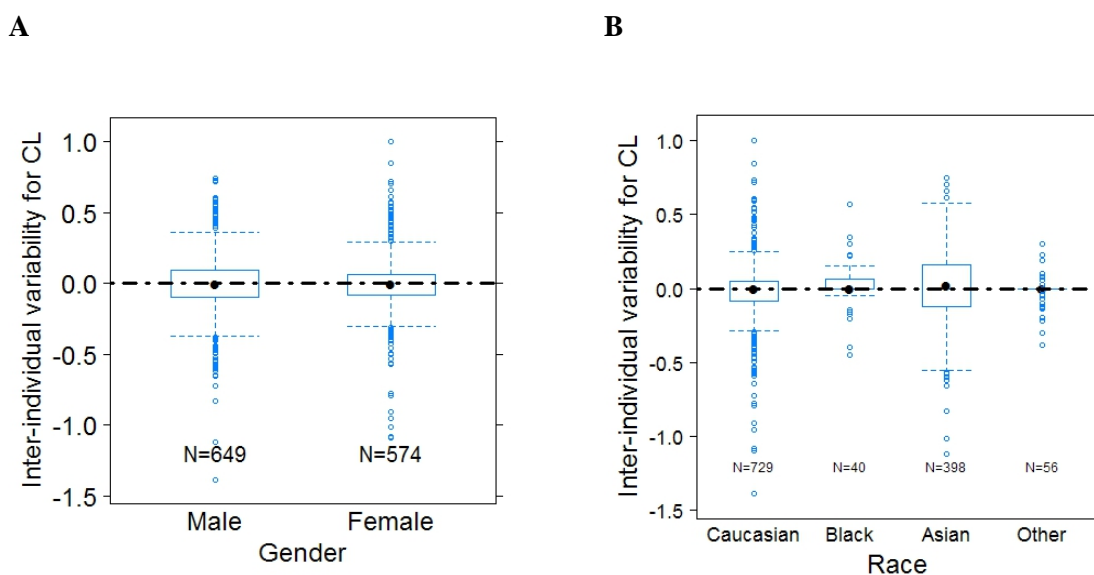


Figure 23 Inter-individual variability on clearance for A) gender B) race.

Table 26 Summary statistics for pharmacokinetic parameters for 20 µg lixisenatide: Healthy subjects by weeks treated and gender (pharmacokinetic population)

	Gender	N	Mean (STD)		Geometric mean (%CV)					Median (range)	
			Weight (kg)	BMI (kg/m ²)	AUC ^a (pg.h/mL)	AUClast (pg.h/mL)	C _{max} (pg/mL)	CL/F (L/h)	V _z /F (L)	t _{1/2z} (h)	t _{max} (h)
Single dose	Female	27	67.0 (7.2)	24.4 (2.5)	733.3 (29.45)	671.5 (32.18)	154.2 (30.27)	27.3 (31.47)	78.4 (39.51)	2.0 (33.38)	1.5 (0.5:3.0)
	Male	31	82.0 (10.1)	25.7 (3.0)	600.9 (34.72)	523.8 (40.76)	106.5 (48.15)	33.3 (35.99)	110.2 (43.15)	2.3 (26.12)	2.0 (1.0:4.0)
Single dose elderly (POP11814)	Female	12	65.6 (6.6)	25.1 (1.8)	963.4 (48.24)	884.3 (46.92)	173.4 (26.50)	20.8 (61.07)	81.8 (41.43)	2.7 (24.60)	1.5 (1.0:3.0)
	Male	6	77.3 (7.9)	26.1 (1.3)	982.9 (23.42)	903.3 (23.64)	152.5 (26.84)	20.3 (27.49)	83.0 (23.91)	2.8 (15.59)	2.0 (1.5:3.0)
Dosing 1-2 weeks	Female	18	65.7 (9.3)	23.5 (2.4)	655.4 (57.01)	598.1 (61.72)	159.4 (32.35)	30.5 (35.62)	-	1.8 (17.86)	1.3 (0.4:2.1)
	Male	35	78.0 (11.2)	24.4 (2.6)	550.2 (45.04)	489.7 (48.93)	117.6 (47.94)	36.3 (42.87)	-	2.1 (171.22)	2.0 (0.5:4.0)
Dosing 4 weeks	Female	31	65.3 (8.4)	24.1 (3.2)	2022.7 (169.21)	1942.0 (170.55)	307.8 (118.46)	9.9 (99.58)	-	4.1 (102.58)	1.6 (0.5:4.1)
	Male	51	81.1 (9.7)	25.4 (2.5)	759.0 (219.49)	707.7 (222.81)	135.2 (121.96)	26.4 (79.64)	-	2.9 (133.01)	1.5 (0.5:6.0)

Single-dose studies in healthy subjects included: PDY11431, PDY11941, POP11814

Multiple-dose studies in healthy subjects included: INT10782, INT10783, TES11807, TES6865

AUC=Area under the concentration versus time curve extrapolated to infinity, AUClast=Area under the plasma concentration versus time curve for time 0 to the last significant (>LOQ) plasma concentration, BMI=Body Mass Index, CL/F=Apparent total body clearance, C_{max}=Maximum plasma concentration observed, CV=Coefficient of variation, N=Number of subjects with available data, STD=Standard deviation, t_{1/2z}=Apparent terminal elimination half-life, t_{max}=Time to maximum plasma concentration, V_z/F=Volume of distribution

^a For multiple dose studies AUC is AUC_{tau} defined for studies INT10782, INT10783, TES6865 and TES11807 as AUC(0-24h).

Studies included with male and female subjects

[Source: Sponsor's Table 45 Page 199, Report 2.7.2 Summary of Clinical Pharmacology Studies]

Table 27 Summary statistics for pharmacokinetic parameters for 20 µg lixisenatide: Healthy subjects by weeks treated, antibody status, and gender (pharmacokinetic population)

	Antibody Status	Gender	N	Mean (STD)		Geometric mean (%CV)				Median (range)	
				Weight (kg)	BMI (kg/m ²)	AUC _{tau} (pg.h/mL)	AUClast (pg.h/mL)	C _{max} (pg/mL)	CL/F (L/h)	t _{1/2z} (h)	t _{max} (h)
Dosing 1-2 weeks	Negative	Female	12	65.3 (9.8)	23.1 (2.0)	727.3 (59.20)	672.8 (63.40)	177.7 (30.01)	27.5 (29.46)	1.8 (19.24)	1.5 (0.5:2.1)
		Male	18	80.0 (10.4)	25.0 (2.6)	535.1 (38.81)	472.6 (40.68)	105.5 (34.28)	37.4 (39.87)	2.4 (182.30)	2.0 (1.0:4.0)
	Positive	Female	6	66.6 (9.1)	24.2 (3.2)	532.2 (31.75)	472.5 (34.47)	128.4 (24.04)	37.6 (36.65)	1.9 (16.30)	1.0 (0.4:2.0)
		Male	17	75.9 (11.9)	23.8 (2.6)	566.8 (50.65)	508.6 (55.48)	131.8 (51.35)	35.3 (47.24)	1.9 (35.57)	1.5 (0.5:3.0)
Dosing 4 weeks	Negative	Female	13	62.9 (7.6)	23.0 (2.8)	731.5 (59.76)	687.4 (58.24)	157.4 (41.21)	27.3 (68.07)	2.1 (26.48)	1.5 (0.5:4.0)
		Male	34	80.4 (8.3)	25.4 (2.6)	481.3 (43.04)	442.8 (43.17)	99.4 (39.78)	41.6 (65.26)	2.3 (25.68)	1.5 (0.5:5.0)
	Positive	Female	17	67.2 (9.0)	24.9 (3.3)	4671.2 (118.88)	4566.7 (119.32)	530.2 (87.94)	4.3 (132.72)	7.0 (74.22)	2.0 (1.0:4.1)
		Male	16	81.5 (11.5)	25.4 (2.4)	2055.8 (138.52)	1975.9 (138.47)	266.5 (93.65)	9.7 (94.77)	4.8 (115.24)	2.0 (0.5:6.0)

Multiple-dose studies in healthy subjects included: INT10782, INT10783, TES11807, TES6865

AUClast=Area under the plasma concentration versus time curve for time 0 to the last significant (>LOQ) plasma concentration, AUC_{tau}=Area under the plasma concentration versus time curve for the dosing interval 0 to tau, tau was defined as 24h, BMI=Body Mass Index, CL/F=Apparent total body clearance,

C_{max}=Maximum plasma concentration observed, CV=Coefficient of variation, N=Number of subjects with available data, STD=Standard deviation,

t_{1/2z}=Apparent terminal elimination half-life, t_{max}=Time to maximum plasma concentration

[Source: Sponsor's Table 46 Page 200, Report 2.7.2 Summary of Clinical Pharmacology Studies]

Table 28 Summary statistics for pharmacokinetic parameters of lixisenatide 20 µg once daily in Chinese subjects: special population by antibody status and gender (pharmacokinetic population) – Study POP11320

Antibody Status	Gender	N	Mean (STD)		Geometric mean (%CV)					Median (range)
			Weight (kg)	BMI (kg/m ²)	AUCtau (pg.h/mL)	AUClast (pg.h/mL)	Cmax (pg/mL)	CL/F (L/h)	t1/2z (h)	
All	Female	10	54.2 (5.7)	21.1 (2.4)	512.6 (78.78)	462.1 (82.42)	136.6 (40.17)	39.0 (40.76)	1.8 (24.68)	1.5 (1.0:3.0)
	Male	11	58.6 (6.1)	21.0 (2.0)	549.2 (27.45)	554.4 (49.01)	159.9 (26.63)	36.4 (24.70)	1.7 (32.59)	1.5 (1.0:2.0)
Negative	Female	5	52.4 (3.3)	20.4 (1.3)	517.7 (30.81)	472.0 (34.57)	147.2 (23.96)	38.6 (27.71)	1.5 (22.54)	1.5 (1.0:3.0)
	Male	9	59.9 (5.8)	21.3 (2.0)	565.7 (28.95)	579.6 (50.35)	158.6 (29.77)	35.4 (28.02)	1.8 (31.09)	1.5 (1.0:2.0)
Positive	Female	5	55.9 (7.4)	21.9 (3.1)	507.6 (101.42)	452.5 (105.92)	126.8 (56.59)	39.4 (49.96)	2.0 (20.02)	1.0 (1.0:2.5)
	Male	2	52.5 (3.5)	19.7 (1.8)	487.8 (5.15)	454.1 (3.85)	166.0 (3.41)	41.0 (5.15)	1.3 (1.39)	1.3 (1.0:1.5)

Multiple-dose studies in healthy subjects included: POP11320

AUClast=Area under the plasma concentration versus time curve for time 0 to the last significant (>LOQ) plasma concentration, AUCtau=Area under the plasma concentration versus time curve for the dosing interval 0 to tau, tau was defined as 24h, BMI=Body Mass Index, CL/F=Apparent total body clearance,

Cmax=Maximum plasma concentration observed, CV=Coefficient of variation, N=Number of subjects with available data, STD=Standard deviation,

t1/2z=Apparent terminal elimination half-life, tmax=Time to maximum plasma concentration

[Source: Sponsor's Table 47 Page 201, Report 2.7.2 Summary of Clinical Pharmacology Studies]

2.4.2 Does renal function affect Lixisenatide pharmacokinetics?

The sponsor conducted a renal impairment study as a single-center, single-dose, parallel group, open-label trial investigating the pharmacokinetic profiles of lixisenatide in four groups of subjects with normal, mild, moderate and severe renal impairment. Lixisenatide was administered as a single dose of 5 µg. The dose was injected subcutaneously, into in the periumbilical abdomen of the trial subjects. The classification of renal impairment was based on creatinine clearance (glomerular filtration rate) estimated with the Cockcroft & Gault formula. The study was conducted prior to the issuance of the new renal impairment guidance by FDA, and therefore used the old cut-off values. It was aimed to have eight subjects in each of the four trial groups in order to cover the complete range of creatinine clearance (Table 29).

Table 29 Classification of renal impairment groups used in Study POP6053

- Renal function group I: 8 subjects with normal renal function creatinine clearance >80 mL/min, matched for age, body mass index (BMI) and gender to the renally compromised groups;
- Renal function group II: 8 subjects with mild RI creatinine clearance 50-80 mL/min;
- Renal function group III: 8 subjects with moderate RI creatinine clearance 30-<50 mL/min;
- Renal function group IV: 8 subjects with severe RI creatinine clearance <30 mL/min, but not requiring hemodialysis and not on dialysis between 2 weeks prior to enrollment visit and end of study.

[Source: report for Sponsor's Study POP6053, page 20]

The sponsor was asked to re-analyze the data based on the current guidance for renal impairment (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf>). The re-analyzed data were submitted by the sponsor on April 5, 2013. The distribution of subjects in each group changed after applying the new classification (Table 30).

Table 30 Classification of Renal Function Based on Estimated Creatinine Clearance (CLcr)

Stage	Description	Classification from 2010		Classification from 1998 and 2004	
		Clcr ¹ (mL/min)	Number of subjects	Clcr ¹ (mL/min)	Number of subjects
1	Control (normal) GFR	≥ 90	4	> 80	8
2	Mild decrease in GFR	≥60 - <90	9	>=50 - <= 80	8
3	Moderate decrease in GFR	≥30 - < 60	11	>=30 - < 50	8
4	Severe decrease in GFR	≥15 - <30	8	< 30	8

¹ CLcr: estimated creatinine clearance based on the Cockcroft-Gault equation

[Source: Sponsor’s Response to Request for Information, Item #5, page 8]

Demographic data, data at baseline, and listing of creatinine clearance provided by the sponsor in report POP6053 is listed in [Table 31](#).

Table 31 Demographic data, data at baseline, and listing of creatinine clearance

Population : Healthy Subjects					Population : Mild RI				
Subject	Gender	Creatinine (Jaffe) (mg/dl)	Creatinine clearance (ml/min)	Body weight (kg)	Subject	Gender	Creatinine (Jaffe) (mg/dl)	Creatinine clearance (ml/min)	Body weight (kg)
276001025	Female	0.78	106.13	89.90	276001003	Female	1.59	40.23	71.30
276001026	Female	0.85	82.41	68.20	276001004	Male	1.32	57.58	76.00
276001027	Male	0.99	135.39	104.9	276001005	Female	0.95	65.95	61.00
276001028	Male	0.98	84.73	84.20	276001007	Male	1.62	73.40	98.40
276001029	Male	0.78	97.80	79.60	276001015	Male	1.51	60.25	65.50
276001030	Male	0.88	85.16	78.20	276001016	Male	1.15	81.71	99.50
276001031	Male	0.99	111.13	86.10	276001017	Male	1.33	83.81	83.60
276001032	Male	0.93	82.92	69.40	276001019	Male	1.32	70.15	81.30
Population : Moderate RI					Population : Severe RI				
Subject	Gender	Creatinine (Jaffe) (mg/dl)	Creatinine clearance (ml/min)	Body weight (kg)	Subject	Gender	Creatinine (Jaffe) (mg/dl)	Creatinine clearance (ml/min)	Body weight (kg)
276001001	Female	1.66	39.94	72.00	276001002	Male	3.53	17.10	62.10
276001006	Male	1.71	51.54	83.50	276001012	Female	3.79	25.82	92.10
276001008	Male	2.16	46.28	104.3	276001014	Male	3.16	28.29	61.90
276001009	Female	2.09	36.29	70.60	276001020	Male	2.67	26.29	72.20
276001010	Male	2.15	41.26	77.90	276001021	Female	3.42	27.40	78.60
276001011	Male	2.76	41.76	90.20	276001022	Female	2.40	27.92	86.00
276001013	Female	1.47	46.49	83.90	276001023	Male	2.73	28.92	74.80
276001018	Male	1.79	42.50	66.80	276001024	Male	2.77	29.49	89.10

[Source: report for Sponsor’s Study POP6053, Listing 14.2.4.2.1, pages 428-431]

Based on Agency’s review of the above data the distribution of subjects in renal function categories were as follows:

Based on CL_{cr} - 4 control (normal) subjects, 10 subjects with mild renal impairment, 10 subjects with moderate renal impairment and 8 subjects with severe renal impairment ([Table 32](#)).

Based on eGFR (MDRD): 1 control (normal) subject, 9 subjects with mild renal impairment, 12 subjects with moderate renal impairment, 8 subjects with severe renal impairment and 2 subjects who would fall under the category of end stage renal disease (ESRD) ([Table 32](#)).

Table 32 Classification of Renal Population Based on Creatinine Clearance and eGFR

Study POP6053: Renal Population Sorted based on eGFR										Study POP6053: Renal Population Sorted based on CLcr										
Subject	Gender	Creatinine (mg/dL)	BW (kg)	Age (y)	MDRD eGFR (mL/min)	CG-CLCr (mL/min)	AUC (pg·h/mL)	AUC _{0-last} (pg·h/mL)	C _{max} (pg/mL)		Subject	Gender	Creatinine (mg/dL)	BW (kg)	Age (y)	MDRD eGFR (mL/min)	CG-CLCr (mL/min)	AUC (pg·h/mL)	AUC _{0-last} (pg·h/mL)	C _{max} (pg/mL)
12	F	3.79	92.1	50	12.61	25.82	505.1	407.3	72.2		2	M	3.53	62.1	70	17.23	17.10	359.0	312.6	66.2
21	F	3.42	78.6	39	14.93	27.40	533.0	491.6	89.7		12	F	3.79	92.1	50	12.61	25.82	505.1	407.3	72.2
2	M	3.53	62.1	70	17.23	17.10	359.0	312.6	66.2		20	M	2.67	72.2	70	23.78	26.29	482.7	443.5	69.7
22	F	2.4	86.0	74	19.73	27.92	299.0	272.2	39.2		21	F	3.42	78.6	39	14.93	27.40	533.0	491.6	89.7
14	M	3.16	61.9	36	22.41	28.29	272.0	235.3	70.1		22	F	2.4	86.0	74	19.73	27.92	299.0	272.2	39.2
24	M	2.77	89.1	74	22.54	29.49	519.9	441.1	57.5		14	M	3.16	61.9	36	22.41	28.29	272.0	235.3	70.1
23	M	2.73	74.8	64	23.61	28.92	205.7	166.6	50.8		23	M	2.73	74.8	64	23.61	28.92	205.7	166.6	50.8
20	M	2.67	72.2	70	23.78	26.29	482.7	443.5	69.7		24	M	2.77	89.1	74	22.54	29.49	519.9	441.1	57.5
11	M	2.76	90.2	48	24.71	41.76		114.8	23.4		9	F	2.09	70.6	49	25.17	36.29	441.9	409.3	79.8
9	F	2.09	70.6	49	25.17	36.29	441.9	409.3	79.8		1	F	1.66	72.0	62	31.30	39.94	484.7	446.9	95.5
8	M	2.16	104.3	71	30.29	46.28	185.6	150.0	27.2		3	F	1.59	71.3	64	32.69	40.23	184.7	167.2	35.4
1	F	1.66	72.0	62	31.30	39.94	484.7	446.9	95.5		10	M	2.15	77.9	58	31.73	41.26	258.5	221.6	37.1
10	M	2.15	77.9	58	31.73	41.26	258.5	221.6	37.1		11	M	2.76	90.2	48	24.71	41.76		114.8	23.4
3	F	1.59	71.3	64	32.69	40.23	184.7	167.2	35.4		18	M	1.79	66.8	58	39.20	42.50	334.2	281.3	42.3
13	F	1.47	83.9	71	35.04	46.49	359.1	312.4	78.5		8	M	2.16	104.3	71	30.29	46.28	185.6	150.0	27.2
18	M	1.79	66.8	58	39.20	42.50	334.2	281.3	42.3		13	F	1.47	83.9	71	35.04	46.49	359.1	312.4	78.5
6	M	1.71	83.5	64	40.50	51.54	285.1	252.2	49.0		6	M	1.71	83.5	64	40.50	51.54	285.1	252.2	49.0
7	M	1.62	98.4	53	44.80	73.40	183.2	142.6	34.3		4	M	1.32	76.0	68	53.94	57.58	320.0	266.2	45.0
15	M	1.51	65.5	40	51.44	60.25	335.1	310.1	80.6		15	M	1.51	65.5	40	51.44	60.25	335.1	310.1	80.6
4	M	1.32	76.0	68	53.94	57.58	320.0	266.2	45.0		5	F	0.95	61.0	53	61.53	65.95	260.3	229.2	59.0
19	M	1.32	81.3	58	55.71	70.15		149.0	31.3		19	M	1.32	81.3	58	55.71	70.15		149.0	31.3
17	M	1.33	83.6	44	58.41	83.81	424.9	372.8	73.5		7	M	1.62	98.4	53	44.80	73.40	183.2	142.6	34.3
5	F	0.95	61.0	53	61.53	65.95	260.3	229.2	59.0		16	M	1.15	99.5	72	62.51	81.71		50.6	44.2
16	M	1.15	99.5	72	62.51	81.71		50.6	44.2		26	F	0.85	68.2	53	69.96	82.41	325.1	278.2	81.9
26	F	0.85	68.2	53	69.96	82.41	325.1	278.2	81.9		32	M	0.93	69.4	60	82.88	82.92	438.0	392.3	106.0
25	F	0.78	89.9	62	74.84	106.13	201.5	174.6	44.7		17	M	1.33	83.6	44	58.41	83.81	424.9	372.8	73.5
28	M	0.98	84.2	69	75.84	84.73	306.7	221.1	38.0		28	M	0.98	84.2	69	75.84	84.73	306.7	221.1	38.0
31	M	0.99	86.1	48	80.68	111.13	170.9	140.4	41.3		30	M	0.88	78.2	71	85.37	85.16	212.7	192.2	66.6
27	M	0.99	104.9	48	80.68	135.39		106.5	21.2		29	M	0.78	79.6	71	98.12	97.80	237.1	174.4	35.6
32	M	0.93	69.4	60	82.88	82.92	438.0	392.3	106.0		25	F	0.78	89.9	62	74.84	106.13	201.5	174.6	44.7
30	M	0.88	78.2	71	85.37	85.16	212.7	192.2	66.6		31	M	0.99	86.1	48	80.68	111.13	170.9	140.4	41.3
29	M	0.78	79.6	71	98.12	97.80	237.1	174.4	35.6		27	M	0.99	104.9	48	80.68	135.39		106.5	21.2
		COUNT	Normal		1							COUNT	Normal		4					
			Mild		9								Mild		10					
			Moderate		12								Moderate		10					
			Severe		8								Severe		8					
			ESRD		2								ESRD		0					

Comparison of pharmacokinetic parameters (geometric mean ratio and 90% CI) between renal function categories is presented in [Table 33](#). The redistribution of subjects based on new FDA renal guidance resulted in imbalances in the number of subjects between different categories, leading to wider confidence intervals on geometric mean ratios.

Table 33 Population effect - Estimate of renal function group ratios of means with 90% confidence intervals (FDA Analysis)

Parameter	Comparison	Estimate (%)	90% CI (%)
C _{max} (pg/mL)	Mild RI/Healthy Subjects	166.02	110.76 - 248.83
	Moderate RI/Healthy Subjects	135.17	89.08 - 205.09
	Severe RI/Healthy Subjects	182.59	124.02 - 268.83
AUC _{last} (pg·h/mL)	Mild RI/Healthy Subjects	140.41	94.31 - 209.16
	Moderate RI/Healthy Subjects	165.63	119.68 - 229.30
	Severe RI/Healthy Subjects	223.79	161.80 - 309.67
AUC (pg·h/mL)	Mild RI/Healthy Subjects	148.22	112.93 - 194.61
	Moderate RI/Healthy Subjects	149.85	113.88 - 197.28
	Severe RI/Healthy Subjects	187.06	139.53 - 250.87

Overall, the average AUC_{0-∞} of lixisenatide was around 48 - 87% higher in the renally impaired subjects than the normal subjects. Plot of lixisenatide AUC_{0-last} as a function of creatinine clearance is shown in [Figure 24](#). Given the imbalance in distribution of subjects across various renal impairment categories, the

distribution shows that lixisenatide exposure increases as creatinine clearance decreases, and no specific out of trend value across the various renal impairment groups was noted.

The geometric mean C_{max} observed in the severe renal impairment group following a dose of 5 μ g administered via SC injection was 62.7 pg/mL. Assuming dose-linearity, a C_{max} of ~250 pg/mL would be expected at 20 μ g dose. This value exceeds the mean value of 209 pg/mL seen in antibody-negative subjects at the supra-therapeutic dose of 30 μ g, as observed by the IRT team in their thorough QT study review. Even though safety information is available from only 4 patients with severe renal impairment enrolled in the Phase III study, it might be possible to dose patients with severe renal impairment at the 10 μ g dose.

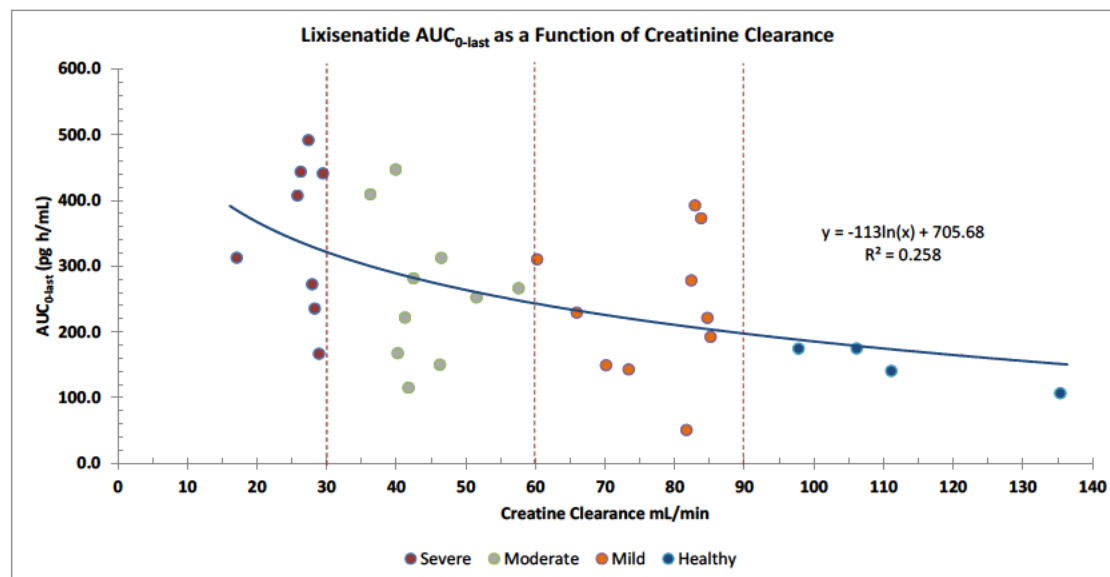


Figure 24 Plot of Lixisenatide AUC_{last} as a Function of Creatinine Clearance

Box plots of C_{max} , AUC_{0-last}, and AUC are presented in [Figures 25](#), [26](#) and [27](#), respectively. Note that the distribution of C_{max} values in patients with severe renal impairment completely overlaps with distribution of C_{max} values in patients with mild and moderate renal impairment. Similarly, the distribution of AUC_{0-t} and AUC_{0-inf} in patients with severe renal impairment also mostly overlaps with the distribution of AUC_{0-t} and AUC_{0-inf} in patients with mild and moderate renal impairment. Further note that the efficacy and safety of lixisenatide in patients with mild and moderate renal impairment have been evaluated in Phase 3 trials, which is discussed later in this section.

C_{max} Comparison:

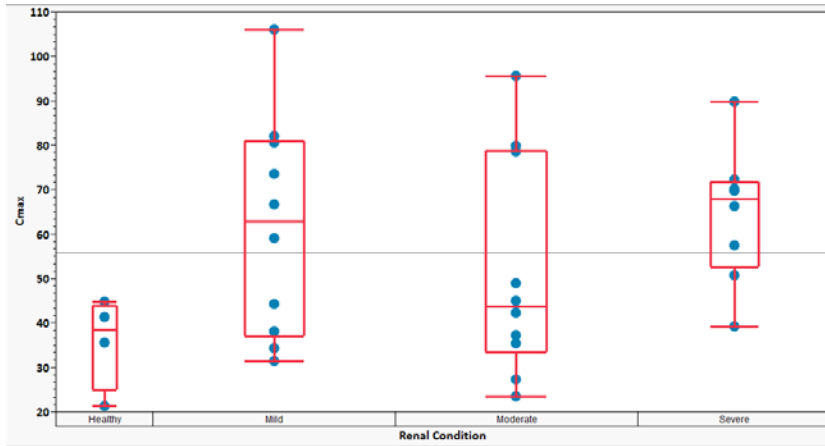


Figure 25 Comparison of C_{max} Across Groups with Different Renal Function

AUC_{0-t} Comparison:

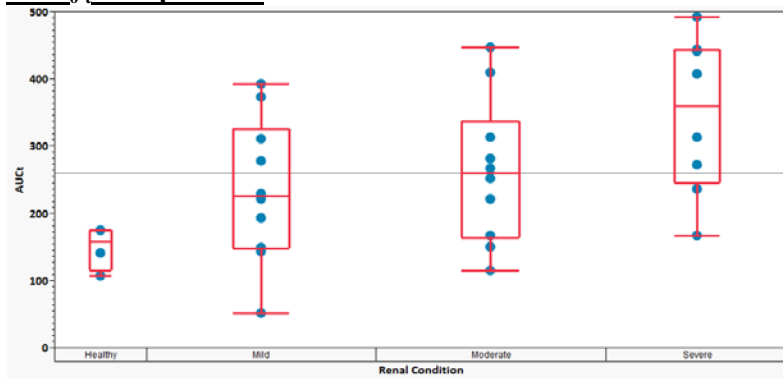


Figure 26 Comparison of AUC_{0-t} Across Groups with Different Renal Function

AUC_{0-inf} Comparison:

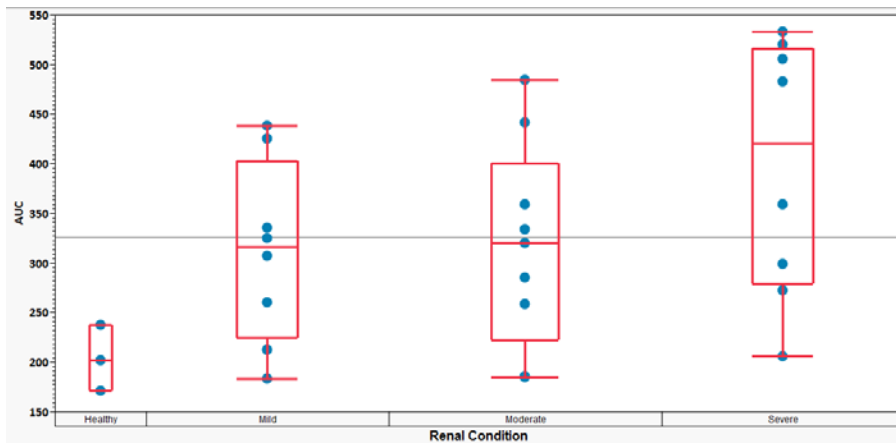


Figure 27 Comparison of AUC_{0-inf} Across Groups with Different Renal Function

Review of Safety data from Phase 3 trials for renally impaired population:

Completed Phase 3 trials did not have any patient with severe renal impairment on lixisenatide treatment. There were approximately 30 moderate renal impairment patients on lixisenatide. A review of safety data in mild renally impaired population from completed Phase 3 trials indicated that there were signs of exaggerated nausea and vomiting and hypoglycemic events ([Figure 28](#)).

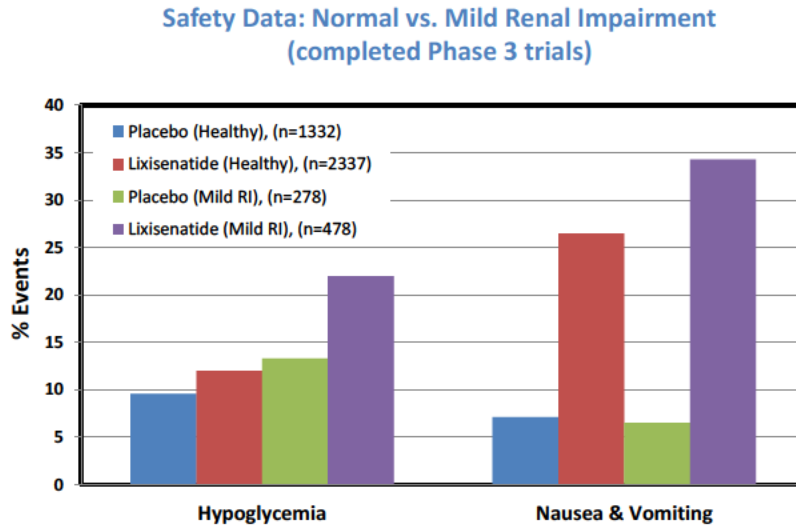


Figure 28 Safety Data in Normal and Mild Renal Impaired Patients from Completed Phase 3 Trials

Lixisenatide was also evaluated in a dedicated efficacy and cardiovascular safety trial (ELIXA) in which patients with moderate renal impairment were also enrolled. Note that in this trial, placebo unadjusted mean treatment effect is almost similar across renal function groups ranging from -0.41 to -0.52. For the placebo-adjusted treatment effect, although confidence limits overlap, mean effects increase progressively with renal impairment from normal to moderate, partly driven by differences in placebo group. The results of this trial demonstrated that reduction in HbA_{1c} for patients with moderate RI was at least similar to or numerically higher than seen in patients with normal renal function based on cross-trial comparison ([Table 34](#) and [Figure 29](#)).

Table 34 Analysis of change from baseline in HbA_{1c} at week 24 (ANCOVA, LOCF) by renal group and subgroup – ITT population

Renal subgroup Treatment group	N	Change From Baseline			
		Mean (SD)	LS Mean (SE) ^a	Diff in LS Mean (SE) ^{ab}	95% CI ^{ab}
≥15 – <30 ml/min/1.73m² (severe renal impairment)					
Placebo	3	0.47 (0.83)	-0.35 (0.000)	-	-
Lixisenatide	3	-1.10 (1.50)	-0.78 (0.000)	-0.43 (0.000)	(NC to NC)
≥30 – <60 ml/min/1.73m² (moderate renal impairment)					
Placebo	261	-0.01 (1.19)	0.04 (0.082)	-	-
Lixisenatide	215	-0.46 (0.93)	-0.43 (0.085)	-0.46 (0.095)	(-0.652 to -0.278)
≥30 – <45 ml/min/1.73m²					
Placebo	69	0.18 (1.01)	0.21 (0.150)	-	-
Lixisenatide	65	-0.50 (1.03)	-0.41 (0.142)	-0.62 (0.174)	(-0.968 to -0.281)
≥45 – <60 ml/min/1.73m²					
Placebo	192	-0.08 (1.25)	-0.05 (0.100)	-	-
Lixisenatide	150	-0.44 (0.88)	-0.45 (0.109)	-0.40 (0.115)	(-0.628 to -0.174)
≥60 – <90 ml/min/1.73m² (mild renal impairment)					
Placebo	549	-0.18 (0.96)	-0.19 (0.045)	-	-
Lixisenatide	560	-0.58 (1.05)	-0.52 (0.045)	-0.33 (0.054)	(-0.436 to -0.223)
≥90 ml/min/1.73m² (no renal impairment)					
Placebo	197	-0.24 (1.05)	-0.21 (0.078)	-	-
Lixisenatide	220	-0.45 (1.17)	-0.42 (0.074)	-0.21 (0.097)	(-0.396 to -0.017)

^a Analysis of covariance (ANCOVA) model with treatment group and region as fixed effects and baseline HbA_{1c} value as a covariate.

^b Difference in LS Mean between lixisenatide and placebo.

Week 24 value is the last observation carried forward (LOCF) before week 24. Patients with both baseline and the Week 24 measurements are included.

Randomization data received: 25JUL2012 / CRF data received: 25JUL2012

Lixisenatide efficacy is preserved in subjects with reduced renal function

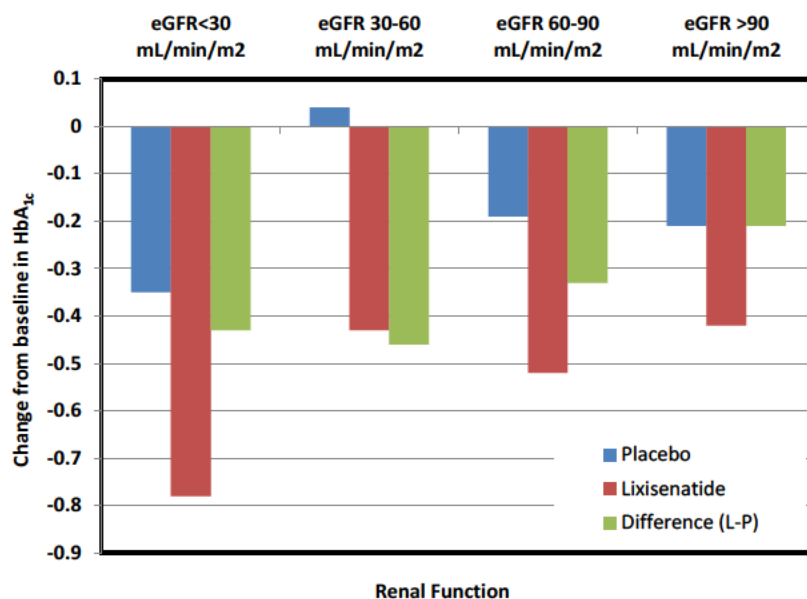


Figure 29 Change in HbA_{1c} in Subjects with Reduced Renal Function in Ongoing Cardiovascular Safety (ELIXA) Trial

An examination of the safety data from the ongoing cardiovascular safety (ELIXA) trial indicated that there was a trend for higher percent of hypoglycemic events as a function of decreased renal function. A similar trend of hypoglycemic events based on renal function was also observed in the placebo group;

however, compared to placebo, a slightly higher number of hypoglycemic events were observed following treatment with lixisenatide (Figure 30).

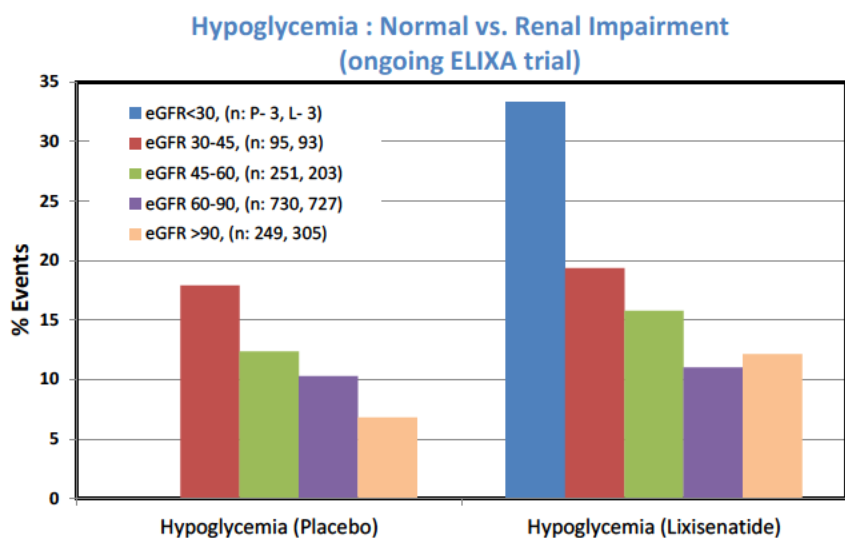


Figure 30 Percent Hypoglycemic Events in Ongoing Cardiovascular Safety (ELIXA) Trial

A similar trend was noted for nausea and vomiting episodes, however, the incidence of nausea and vomiting was much higher following lixisenatide treatment compared to placebo (Figure 31).

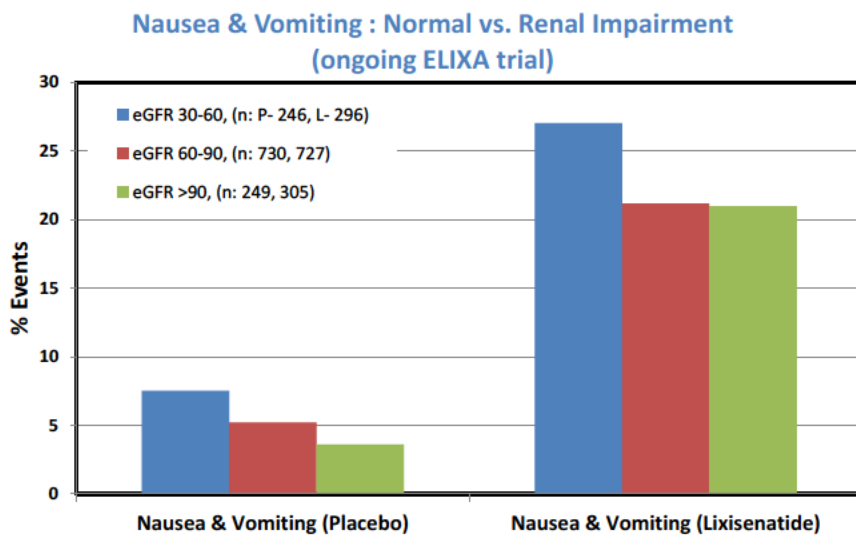


Figure 31 Percent Nausea & Vomiting Events in Ongoing Cardiovascular Safety (ELIXA) Trial

Reviewer’s Comments:

In subjects with mild renal impairment, C_{max} was about 66% higher and AUC was up to 48% higher in contrast to healthy subjects. No dose adjustment is recommended in these patients, however, use with caution is recommended because of exaggerated hypoglycemia, nausea and vomiting observed in Phase 3

trials.

In subjects with moderate renal impairment, C_{max} was about 35% higher and AUC was up to 65% higher in contrast to healthy subjects. There were no unique safety concerns observed in patients with moderate renal impairment from the ongoing cardiovascular safety trial. No dosing adjustment is recommended in patients with moderate RI; however, use with caution is recommended because of general concerns of dehydration leading to acute renal failures with this class of drugs. Please refer to the clinical review by Dr. Suchitra Balakrishnan for complete details of the results from efficacy and safety trial patients with moderate RI.

In subjects with severe renal impairment, C_{max} was about 82% higher and AUC was up to 123% higher in contrast to healthy subjects. There were only 3 patients with severe RI in the efficacy and safety trial evaluating the use of lixisenatide in RI. The sponsor proposed not to use lixisenatide in patients with severe RI. However, given that efficacy of lixisenatide is preserved in patients with RI and that there is no unique safety concerns in this population, this reviewer recommends that lixisenatide should be used with caution in patients with severe RI. The dose of lixisenatide should be restricted to 10 μg QD in patients with severe RI, and should be increased to 20 μg QD only in patients tolerating lixisenatide who require additional glycemic control.

The recommendation for 10 μg QD dose in patients with severe RI is based on exposure matching. A forest plot with the recommendations is shown in [Figure 32](#).

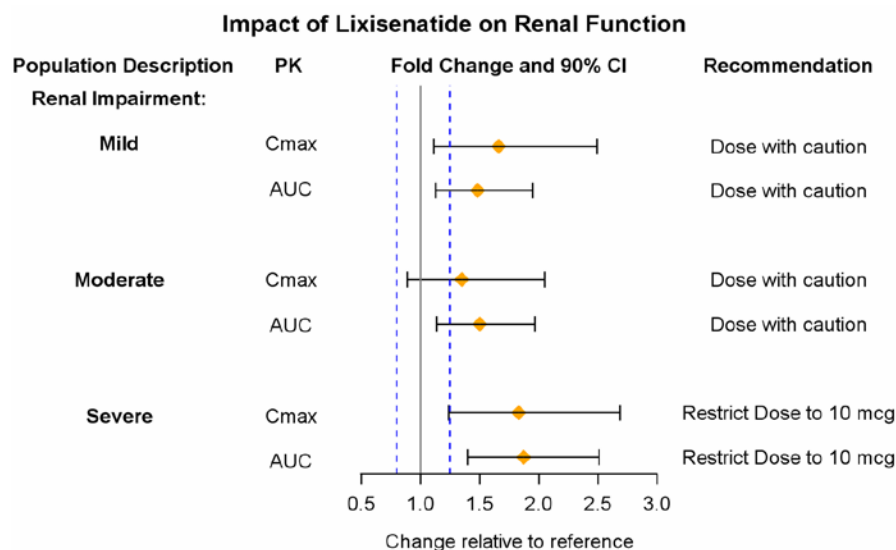


Figure 32 Effect of Renal Impairment on Lixisenatide PK

(Dashed line indicate the 80%-125% limit)

2.4.3 Does hepatic dysfunction affect Lixisenatide pharmacokinetics?

Lixisenatide is cleared primarily by the kidney; hence hepatic dysfunction is not expected to affect the PK of lixisenatide to any relevant degree. In addition, lixisenatide exhibits only a moderate degree of protein binding (~55%) to human plasma proteins. There is therefore no relevant binding of lixisenatide to albumin, the plasma content of which is affected by hepatic impairment.

The sponsor did not conduct any PK study in subjects with acute or chronic hepatic impairment. Advanced hepatic impairment was an exclusion criterion in the clinical studies.

Reviewer’s Comments:

No dosing adjustment is recommended in patients with hepatic impairment. This is similar to the dosing recommendation for other biologics.

2.5 Extrinsic Factors

2.5.1 What is the effect of different injection sites on the bioavailability of Lixisenatide?

The relative bioavailability of lixisenatide after SC administration in the thigh, upper arm and abdomen was assessed in a randomized, open-label, single-center, three period, cross-over trial (Study BDR6864) where single doses of lixisenatide were administered SC to 43 healthy male and female obese subjects, 18 to 65 years old, on three different occasions, each separated by a 48 hour wash-out period counting from time of dosing. The site of administration differed between the dosing days, either in the abdomen, thigh or upper arm. The dose was given as a fixed dose (10 µg) in a fixed volume (100 µl). The pharmacokinetic parameters are summarized in [Table 35](#), and statistical analysis is presented in [Table 36](#) below. The pharmacokinetic profile of lixisenatide is presented in [Figure 33](#).

Table 35 Effect of injection site on lixisenatide pharmacokinetics after single 10 µg SC administration in thigh, abdomen, and upper arm in healthy obese male and female subjects

PK Parameter	Mean ± SD (CV%) [Geometric Mean] ^a		
	Treatment A: Abdomen (N=42)	Treatment B: Thigh (N=43)	Treatment C: Arm (N=42)
C _{max} (pg/mL)	60.3 ± 21.1 (35) [56.7]	51.4 ± 16.9 (33) [48.6]	60.5 ± 22.8 (38) [56.9]
t _{max} (h) ^a	2.00 (0.50 , 4.00)	2.50 (0.50 , 4.05)	2.00 (0.50 , 5.00)
t _{1/2z} (h)	3.15 ± 2.18 (69) [2.81]	3.57 ± 1.65 (46) [3.29]	2.88 ± 0.946 (33) [2.77]
AUC _{clast} (h.pg/mL)	283 ± 126 (45) [253]	286 ± 131 (46) [252]	296 ± 122 (41) [268]
AUC (h.pg/mL)	396 ± 121 (31) [378]	410 ± 143 (35) [385]	391 ± 127 (32) [371]
t _{lag} (h) ^a	0.00 (0.00 , 1.00)	0.00 (0.00 , 0.50)	0.00 (0.00 , 1.00)

^a For t_{max} and t_{lag}, values are median (min, max).

CV = coefficient of variation; N = number of subjects exposed; PK = pharmacokinetic(s); SD = standard deviation.

[Source: Sponsor’s report bdr6864, Table 21, page 63]

Table 36 Ratio estimates with 90% confidence limits for treatment differences

Parameter	Treatment comparison	Estimate	90% CI
C_{max} (pg/mL)	B/A	0.86	(0.79, 0.94)
	C/A	1.00	(0.92, 1.09)
AUC _{last} (pg.h/mL)	B/A	1.00	(0.88, 1.14)
	C/A	1.06	(0.93, 1.21)
AUC (pg.h/mL)	B/A	1.02	(0.90, 1.14)
	C/A	0.99	(0.89, 1.11)

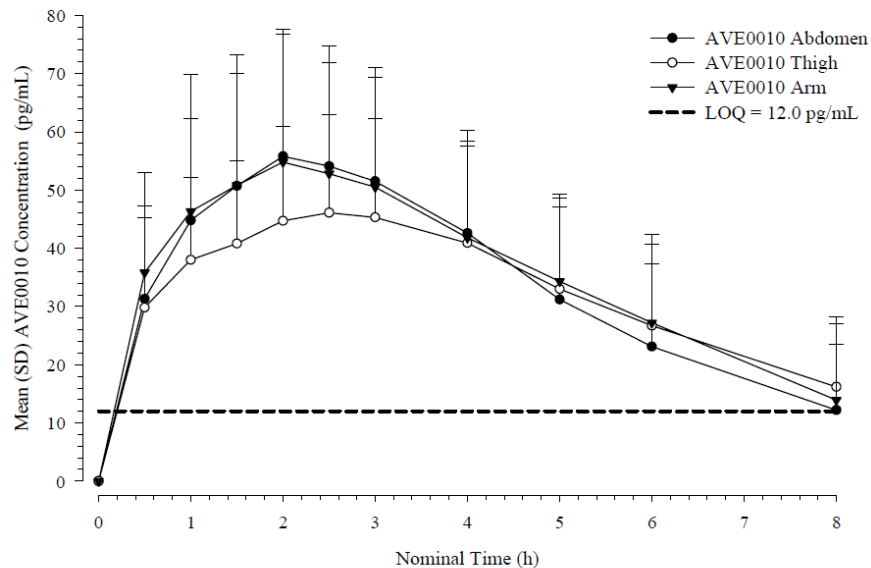
Treatment A: 10 µg SC administration in the abdomen.

Treatment B: 10 µg SC administration in the thigh.

Treatment C: 10 µg SC administration in the arm.

CI = confidence interval.

[Source: Sponsor's report bdr6864, Table 21, page 64]



SD = standard deviation; LOQ = limit of quantification;

Figure 33 Mean (SD) lixisenatide plasma concentrations from different injection sites

[Source: Sponsor's report bdr6864, Figure 1, page 62]

A single SC injection of 10µg lixisenatide in the abdomen, the thigh, or the arm resulted in comparable bioavailability. Analyses of AUC_{last} and AUC showed no differences between the 3 injection sites based on the ratio estimates and the 90% CIs, which were within the equivalence range of 80% to 125%. However, the mean C_{max} following SC injection in the thigh was slightly lower compared to the injection in the abdomen (90% CI for the ratio: [0.79, 0.94]), whereas the mean C_{max} value for the injection in the arm was similar to that of the abdomen. However, this decrease in C_{max} is not likely to have a clinical impact on the efficacy of lixisenatide or its safety/tolerability profile. Based on these findings lixisenatide can be administered interchangeably at these injection sites.

2.5.2 Drug-Drug Interactions

2.5.2.1 What is the CYP inhibition potential of Lixisenatide?

The potential inhibitory effect of lixisenatide on the important human drug metabolizing cytochrome P450s, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A were assessed *in vitro* in a pooled microsomal preparation from 50 human livers in study MIH0332. The model substrates used were as follows: phenacetin (CYP1A2), bupropion (CYP2B6), diclofenac (CYP2C9), S-mephenytoin (CYP2C19), dextromethorphan (CYP2D6), midazolam and testosterone (CYP3A4). The summary of estimated IC₅₀ values for lixisenatide for human drug metabolizing cytochrome P450s is presented in [Table 37](#) below. At the maximum tested concentration of 20 µmol/L (97 µg/mL), the observed percent inhibition ranged from 0-32%, indicating that the IC₅₀-values for the inhibition of human CYP enzymes by lixisenatide are above 20 µmol/L. Thus, lixisenatide is not expected to cause any drug-drug interactions related to inhibition of cytochrome P450s and we agree with the sponsor's conclusions. In addition, the inhibitory effect of lixisenatide on human cytochrome P450 isozyme CYP2C8 was determined in human liver microsomes in study MIH0544.

Table 37 *In vitro* CYP enzyme inhibition potential of lixisenatide

CYP Enzyme	Probe Substrate	IC ₅₀ (µmol/L)	Inhibition at 20 µmol/L AVE0010 (%) ¹
CYP1A2	Phenacetin	> 20	11
CYP2B6	Bupropion	> 20	9
CYP2C9	Diclofenac	> 20	0
CYP2C19	(S)-Mephenytoin	> 20	32
CYP2D6	Dextromethorphan	> 20	4
CYP3A	Midazolam	> 20	10
CYP3A	Testosterone	> 20	20

¹ relative to control without AVE0010

[Source: Sponsor's report mih0332, Table 6, page 19]

Enzyme	Test Substrate	IC ₅₀ (µmol/L) AVE0010
CYP2C8	Paclitaxel	> 200

[Source: Sponsor's report mih0544, page 15]

The sponsor also examined the *in vitro* induction potential of lixisenatide for CYP1A, CYP2B6, CYP2C9 and CYP3A in primary cultures of human hepatocytes over the lixisenatide concentration range 0.037 – 37 nM (180 - 180000 pg/mL). No *in vitro* induction potential for CYP1A, CYP2B6, CYP2C9 and CYP3A was observed for lixisenatide over the concentration range 0.037 – 37 nM (180 - 180000 pg/mL) both at the enzyme activity and mRNA level.

The sponsor proposed that *in vivo* drug interactions due to induction of CYP1A, CYP2B6, CYP2C9 and CYP3A by lixisenatide in plasma up to concentrations of 37 nM (180000 pg/mL) are considered unlikely. This reviewer agrees with the sponsor.

2.5.2.2 What is the effect of Lixisenatide co-administration on the pharmacokinetics of other drugs?

Several drug interactions were evaluated by the sponsor with an objective to establish the effect of lixisenatide on gastro-intestinal motility and how it impacts the pharmacokinetic profile of other drugs, especially those sensitive to these physiological changes.

2.5.2.2.1 Acetaminophen

This drug-drug interaction study assessed the effect of a 10 µg injection of lixisenatide on the pharmacokinetic (PK) parameters of a single dose of oral acetaminophen. This single-center, single-dose, open-label, randomized, placebo-controlled, 5-treatment, 5-period, 5-sequence crossover study was conducted in 15 healthy male and female subjects aged between 18 and 65 years, with body weight between 50 and 90 kg (males) or 40 and 80 kg (females) and a body mass index (BMI) between 18 and 35 kg/m².

A single dose (1000 mg) of acetaminophen was administered at -1 hour, +1 hour and, +4 hours relative to lixisenatide administration and -1 hour and +1 hour relative to placebo administration. There was at least a 2-day washout between each acetaminophen administration period. The treatments were administered as shown in [Table 38](#).

Table 38 Lixisenatide and Acetaminophen Treatments and conditions of administration

Treatments	Day 1						
	7:00 AM	8:00 AM	8.30 AM	9:00 AM	12:00 PM	1.30 PM	8.30 PM
A	AA adm.	Placebo injection	Breakfast			Lunch	Dinner
B	AA adm.	AVE0010 injection	Breakfast			Lunch	Dinner
C		AVE0010 injection	Breakfast	AA adm.		Lunch	Dinner
D		AVE0010 injection	Breakfast		AA adm.	Lunch	Dinner
E		Placebo injection	Breakfast	AA adm.		Lunch	Dinner

AA adm. = acetaminophen administration

[Source: sponsor's study INT6863, Table 3, Page 25]

Mean (SD) acetaminophen plasma concentration-time profiles for each treatment are shown in [Figure 34](#).

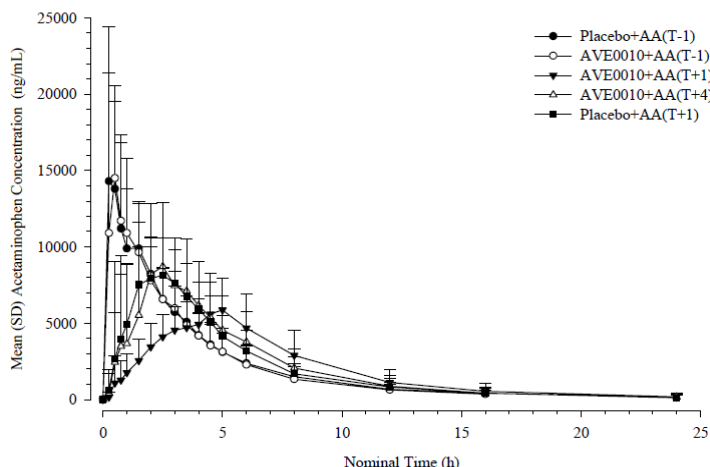


Figure 34 Mean (SD) acetaminophen plasma concentrations

[Source: sponsor's study INT6863, Figure 1, Page 65]

Treatment A, where acetaminophen was given 1.5 hours before breakfast, 1 hour before placebo served as the control arm for this study. Comparison of Treatment E (acetaminophen given 30 minutes after breakfast, 1 hour after placebo) and Treatment A allowed the assessment of the effect of food on acetaminophen. When acetaminophen was administered 30 minutes following breakfast, there was a 48% reduction of C_{max} and a corresponding increase of median t_{max} from 0.25 to 2 hours.

When acetaminophen was administered 1 hour before lixisenatide (1.5 hours before breakfast) in Treatment B, there was no change in the rate and extent of absorption of acetaminophen compared to treatment A.

When acetaminophen was administered 1 hour after lixisenatide administration (30 minutes post breakfast), there was a 63% reduction in C_{max} and a corresponding shift in T_{max} from less than 1 hour to 4.5 hours. However, treatment C reflects the composite effect of food on acetaminophen, and the delaying effect of lixisenatide on gastric emptying. Accounting for the effect of food on acetaminophen (treatment E), resulted in a 15% reduction of acetaminophen C_{max} due to delayed gastric emptying effect of lixisenatide.

Acetaminophen PK parameter ratio estimates with 90% CIs for treatment differences are reported in [Table 39](#).

Table 39 Ratio estimates with 90% CIs for treatment differences

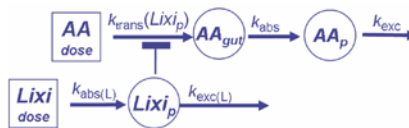
Parameter	Treatment comparison	Ratio	
		Estimate	90% CI
AUC	B versus A	0.97	(0.92, 1.02)
	C versus A	0.87	(0.83, 0.92)
	D versus A	0.95	(0.91, 1.00)
	E versus A	0.92	(0.87, 0.96)
	B versus E	1.06	(1.01, 1.11)
	C versus E	0.95	(0.91, 1.00)
	D versus E	1.04	(0.99, 1.09)
AUC _{last}	B versus A	0.97	(0.93, 1.02)
	C versus A	0.88	(0.83, 0.92)
	D versus A	0.96	(0.91, 1.01)
	E versus A	0.92	(0.88, 0.97)
	B versus E	1.05	(1.01, 1.10)
	C versus E	0.95	(0.90, 0.99)
	D versus E	1.04	(0.99, 1.09)
C _{max}	B versus A	0.97	(0.78, 1.19)
	C versus A	0.37	(0.30, 0.45)
	D versus A	0.69	(0.56, 0.85)
	E versus A	0.52	(0.42, 0.64)
	B versus E	1.85	(1.50, 2.28)
	C versus E	0.71	(0.57, 0.87)
	D versus E	1.32	(1.07, 1.63)

AUC = area under the curve; CI = confidence interval.
 Treatments: A: Placebo + Acetaminophen 7 AM (T-1h)
 B: AVE0010 + Acetaminophen 7 AM (T-1h)
 C: AVE0010 + Acetaminophen 9 AM (T+1h)
 D: AVE0010 + Acetaminophen 12 AM (T+4h)
 E: Placebo + Acetaminophen 9 AM (T+1h)
 Note: Breakfast was administered at 8:30 AM, lunch at 1:30 PM, and dinner at 6:30 PM

[Source: sponsor’s study INT6863, Table 21, Page 71]

- Statistical analysis performed by the sponsor on acetaminophen PK parameters showed that regardless of the dose-timing of lixisenatide (1 hour before and 1 hour and 4 hours after acetaminophen dosing), the AUC of acetaminophen was not affected by the administration of lixisenatide.
- Sponsor also reported that the Wilcoxon sign-rank test for the difference between treatments in t_{max} showed statistically significant results for each of the pairwise comparisons with the exception of the comparisons of treatment A versus B and D versus E.

Note that the recommended maintenance dose of lixisenatide is 20 µg. Therefore, utilizing the results of this study, the sponsor tried to develop a model to support the estimation of the effect of 20 µg on the absorption of acetaminophen and also assess the effect of lixisenatide on gastric emptying of drugs with varying elimination half-lives.



Description of model:

A given dose of acetaminophen (AA_{dose}) transits from the stomach into the small intestine (AA_{gut}) from where it is absorbed into the blood stream (AA_p). From this central compartment acetaminophen is removed with the elimination rate k_{exc} . The transit of acetaminophen from the stomach into the gut, represented as k_{trans} , is inhibited by lixisenatide. This inhibitory effect of lixisenatide on this transit rate is represented as a sigmoidal Hill function. Pharmacokinetics of lixisenatide are modeled as a simple one-compartment model, where the lixisenatide dose ($Lixi_{dose}$) is directly absorbed into the central

compartment ($Lixi_p$) from where it is eliminated subsequently.

Reviewer Comments on pharmacokinetic model:

The main concern with this model is that it was developed based on the mean data and does not account for individual variability. In the current model, to extrapolate the effect of 20 µg dose of lixisenatide on GI emptying, sponsor assumed that the effect of 20 µg lixisenatide on k_{trans} is same as the 10 µg lixisenatide dose and made predictions for effect on k_{trans} based on mean PK profile of 20 µg dose. A better way would be to fit the model accounting for variability and develop a relationship between exposure and k_{trans} , which in turn can be used to determine the effect of 20 µg lixisenatide dose. This information has been requested from sponsor and will be documented in an addendum to this review.

There are some other limitations as discussed below:

- (a) Effect of lixisenatide on drugs that have a short t_{max} similar to acetaminophen, but do not exhibit food-effect is unknown*
- (b) Effect of lixisenatide on drugs that are absorbed slowly (longer t_{max}), or that are intentionally formulated to be absorbed at a pH higher than the stomach (e.g. enteric coated formulations) is unknown*
- (c) Co-administration of lixisenatide with metformin is a very likely scenario in this population, and it is not known from this model if and to what extent lixisenatide will influence the absorption of metformin from gastro-retentive formulations; however, this co-administration may have been evaluated in Phase 3 trials*
- (d) It is not known how delayed gastric emptying would affect co-administered drugs which are metabolized through CYP mediated pathways.*

Reviewer Comments on results of the study:

This study clearly demonstrated that a 10 µg dose of lixisenatide can have a delaying effect of up to 4 hours on absorption of drugs such as acetaminophen which are absorbed rapidly with a short t_{max} (1-3 hours). Oral medications that are dependent on threshold concentrations for efficacy, such as antibiotics, should be taken at least 1 hour before lixisenatide injection or with a meal or snack when lixisenatide is not administered.

2.5.2.2.2 Warfarin

This drug-drug interaction study assessed the effect of repeated subcutaneous daily doses of 20 µg lixisenatide on the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of S-warfarin, in healthy male subjects.

The study design was as follows:

Treatment A: Warfarin was administered on Day 1 without concomitant lixisenatide treatment.

Treatment B: Warfarin was administered on Day 11 with concomitant lixisenatide treatment (=fourth day of 20 µg dose).

Warfarin (25 mg QD) was administered as a single dose on Day 1 of Period 1 and day 11 of Period 2. Lixisenatide was administered in Period 2 with a dose of 10 µg on days 1-7 and 20 µg QD on days 8-14. Lixisenatide was administered 30 minutes before breakfast while warfarin was administered with breakfast. The mean concentration profiles for (S)-warfarin, (R)-warfarin and lixisenatide are shown in [Figure 35](#) below.

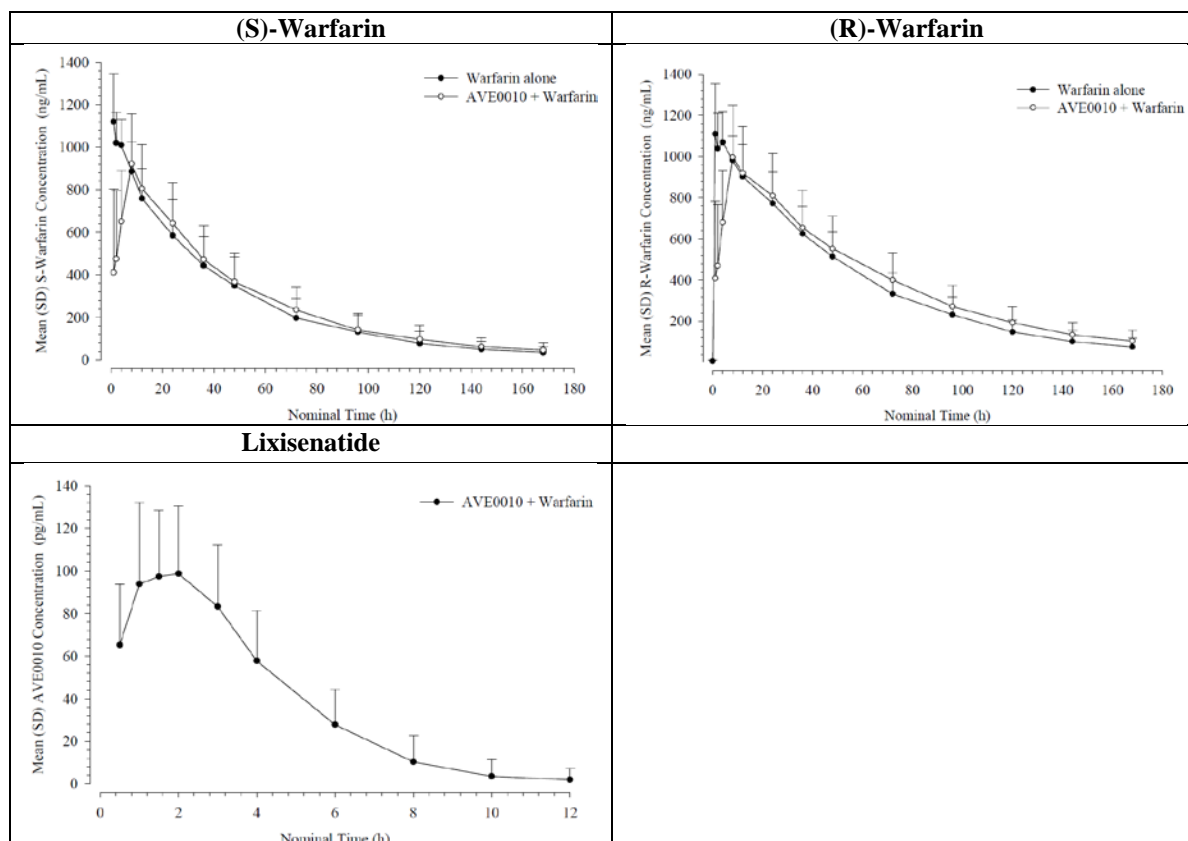


Figure 35 Pharmacokinetic profiles of (S)-warfarin, (R)-warfarin and lixisenatide

[Source: Sponsor's report int10408, Figures 6, 8, 10, pages 69, 71, 72]

Statistical analysis of pharmacokinetic parameters summarized in [Table 40](#) below for S-warfarin and [Table 41](#) for R-warfarin showed that the 90% CIs for AUC_{last} and AUC of S-warfarin and R-warfarin were within the protocol-specified range of 80- 125%, demonstrating the lack of pharmacokinetic interaction on systemic exposure. The geometric mean C_{max} of S-warfarin was 0.81, with 90% confidence intervals ranging from 0.68-0.96, and the geometric mean C_{max} of R-warfarin was 0.85, with 90% confidence intervals ranging from 0.70-1.02. However, the appearance of pharmacokinetic interaction on C_{max} could be due to a potential outlier. Excluding that subject's C_{max} value from the overall data increased the geometric mean ratio of C_{max} for S-warfarin to 0.88, and that for R-warfarin to 0.94, with a 90% confidence interval ranging from 0.82-0.95 for S-warfarin, and 0.88-0.99 for R-warfarin, indicating a lack of significant pharmacokinetic interaction also for the rate of exposure in this case. There was, however, a shift in T_{max} from 1 hour post warfarin alone treatment to 8.0 hours post warfarin+lixisenatide treatment.

Table 40 Treatment ratio estimates of warfarin plus lixisenatide versus warfarin alone with 90% confidence interval (analysis for pharmacokinetic population) – S-warfarin

Parameter	Comparison	Estimate	90% CI
C _{max} (ng/mL)	Warfarin+AVE0010 QD versus Warfarin alone	0.81	(0.68 to 0.96)
AUC _{last} (h.ng/mL)	Warfarin+AVE0010 QD versus Warfarin alone	1.01	(0.85 to 1.21)
AUC (h.ng/mL)	Warfarin+AVE0010 QD versus Warfarin alone	1.03	(0.87 to 1.22)

PK parameters are for S-warfarin.

[Source: Sponsor's report int10408, Table 22, page 76]

Table 41 Treatment ratio estimates of warfarin plus lixisenatide versus warfarin alone with 90% confidence interval (analysis for pharmacokinetic population) – R-warfarin

Parameter	Comparison	Estimate	90% CI
C _{max} (ng/mL)	Warfarin+AVE0010 QD versus Warfarin alone	0.85	(0.70 to 1.02)
AUC _{last} (h.ng/mL)	Warfarin+AVE0010 QD versus Warfarin alone	1.03	(0.86 to 1.22)
AUC (h.ng/mL)	Warfarin+AVE0010 QD versus Warfarin alone	1.06	(0.90 to 1.26)

PK parameters are for R-warfarin.

[Source: Response to Agency request for information (Agency email dated 14-Aug-2013) received 21-Aug-2013, Table 1, page 5]

Plots of average INR over C_{max} of lixisenatide in plasma and AUC_(0-τ) of lixisenatide are presented in [Figure 36](#). These plots combine the INR values from both when warfarin was given alone and when warfarin and lixisenatide were given together. Average INR values for warfarin alone treatment are presented at the C_{max} and AUC values that were set to zero. These are then connected to the values of average INR observed when warfarin and lixisenatide were given together.

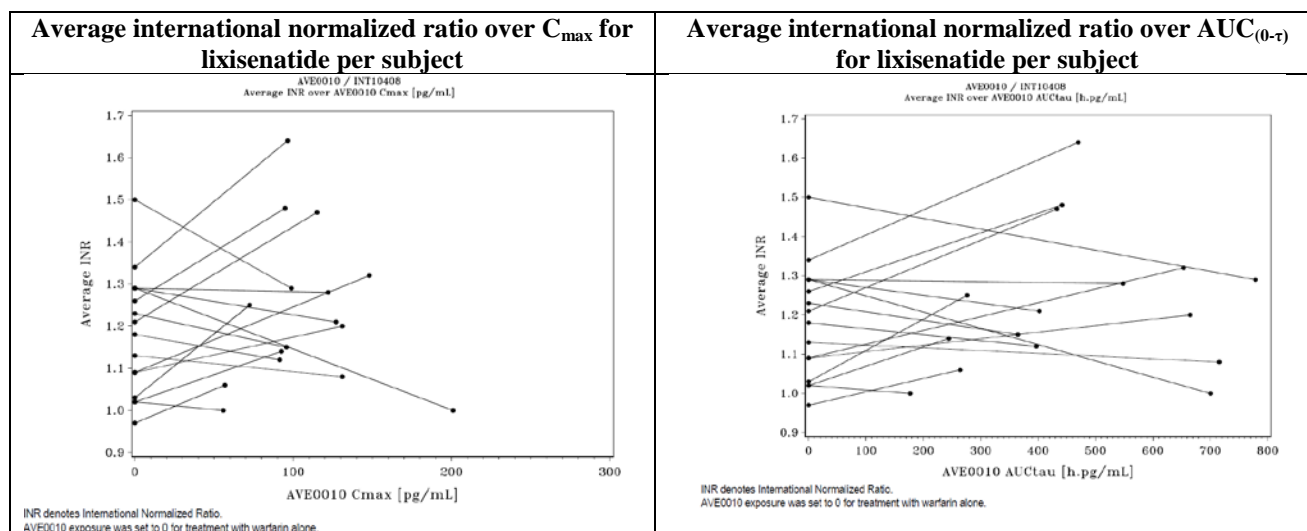


Figure 36 Average international normalized ratio over C_{max} and AUC_(0-τ) for lixisenatide per subject

[Source: Sponsor's report int10408, Figures 16,17, pages 80, 81]

The pharmacodynamic effect of warfarin as determined by INR profiling did not suggest an impact of concomitant lixisenatide treatment. The maximum observed change in INR was change from 1.35 to 1.65.

Reviewer Comments:

The implication of the 7-hour delay in time to peak warfarin concentration when administered 30 minutes after lixisenatide is unknown. While no dose adjustment for warfarin is required when co-administered with lixisenatide based on lack of pharmacokinetic interaction, frequent monitoring of INR in patients on warfarin and/or coumarin derivatives, as well as following of instructions in the warfarin product monograph for appropriate monitoring and dose adjustment is recommended at the time of initiation or ending of lixisenatide treatment.

2.5.2.2.3 Atorvastatin

This study investigated the effect of multiple doses of lixisenatide on the pharmacokinetics of multiple doses of atorvastatin given in the morning or evening. In Period 1, 40 mg atorvastatin was administered 30 minutes post-breakfast during days 1-6 for Group A, or 11.5 hrs post-breakfast during days 1-6 for group B. There was no lixisenatide treatment in Period 1. Following a 5-day washout period, in Period 2, for the AM group, lixisenatide was administered at 7:30 each morning (10 µg QD for days 1-7 followed by 20 µg QD for days 8-14) followed by breakfast at 8:00 AM and then atorvastatin at 8:30 AM. For the PM group, lixisenatide was administered at 7:30 each morning (10 µg QD for days 1-7 followed by 20 µg QD for days 8-15) followed by breakfast at 8:00 AM and then atorvastatin at 8:00 PM (2 hours post dinner).

The mean concentration profiles for atorvastatin, p-OH-atorvastatin, o-OH-atorvastatin and lixisenatide when co-administered at steady state conditions for the AM and PM groups are presented in [Figure 37](#), and the mean pharmacokinetic parameters are presented in [Table 42](#) below.

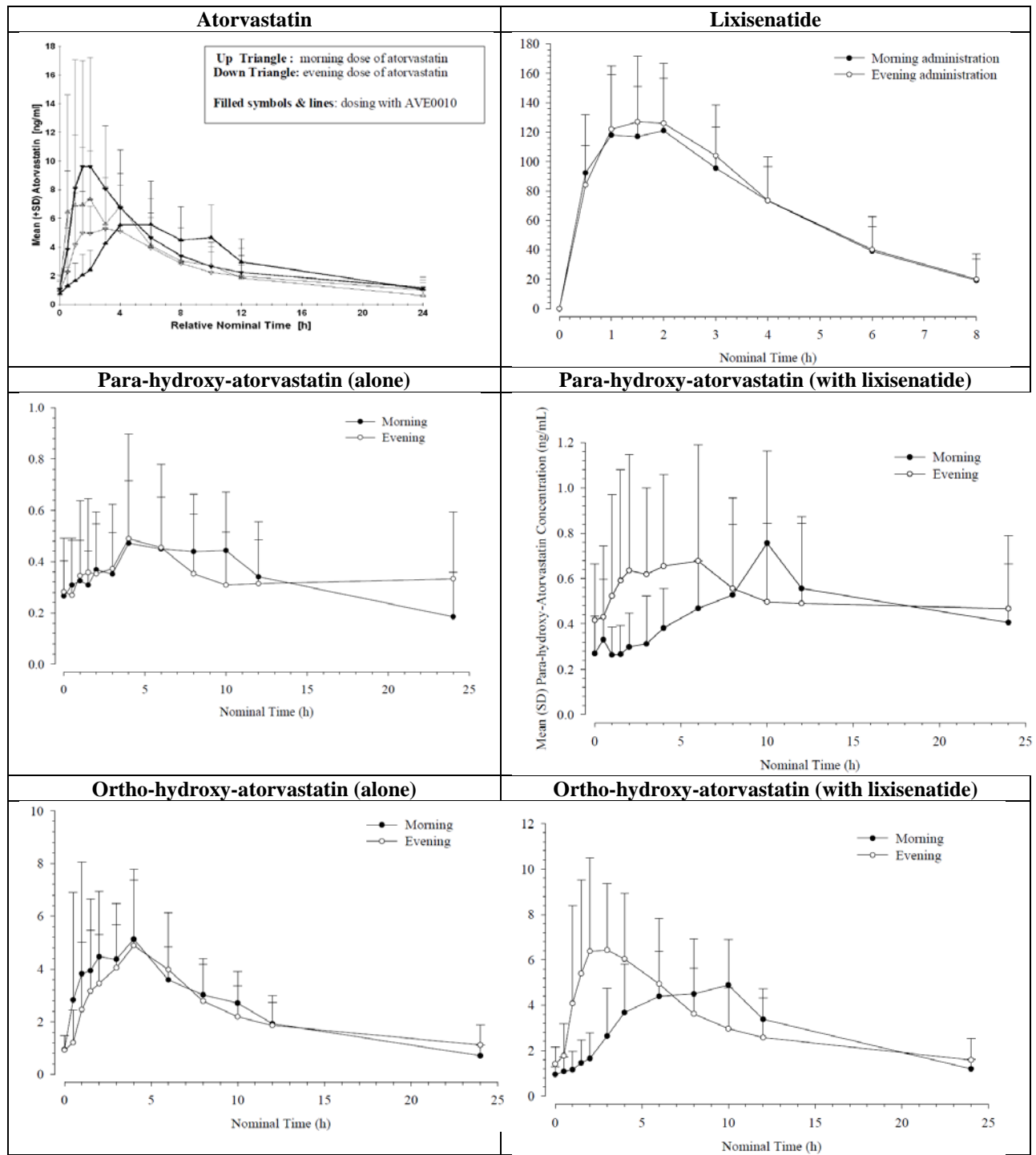


Figure 37 Mean concentration-time profiles for the co-administered drugs

[Source: Sponsor's report int10409, Figures 1, 3-7 pages 70-74]

Table 42 Pharmacokinetic Parameters of Atorvastatin, Para-hydroxy-atorvastatin, and Ortho-hydroxy-atorvastatin (Atorvastatin Administered Alone OR Administered With Lixisenatide)

Atorvastatin administered alone				Atorvastatin administered with Lixisenatide					
Atorvastatin									
PK Parameter	Morning		Evening		PK Parameter	Morning		Evening	
C _{max} (ng/mL)	11.2 ± 7.02 (62)	[9.65]	7.47 ± 3.42 (46)	[6.75]	C _{max} (ng/mL)	7.50 ± 4.40 (59)	[6.62]	14.0 ± 9.15 (66)	[11.3]
t _{max} (h)	1.50 (0.50 , 4.00)		2.00 (1.00 , 4.00)		t _{max} (h)	4.03 (0.50 , 10.03)		1.76 (1.00 , 4.02)	
t _{1/2z} (h)	6.53 ± 1.34 (21)	[6.41]	13.3 ± 5.78 (43)	[12.3]	t _{1/2z} (h)	7.57 ± 3.17 (42)	[7.18]	12.7 ± 5.63 (44)	[11.6]
AUC _{0-τ} (h.ng/mL)	67.9 ± 30.1 (44)	[62.8]	60.3 ± 32.9 (55)	[53.2]	AUC _{0-τ} (h.ng/mL)	73.4 ± 33.6 (46)	[67.8]	80.3 ± 44.7 (56)	[69.9]
Para-hydroxy-atorvastatin									
PK Parameter	Morning		Evening		PK Parameter	Morning		Evening	
C _{max} (ng/mL)	0.548 ± 0.242 (44)	[0.502]	0.540 ± 0.420 (78)	[0.426]	C _{max} (ng/mL)	0.798 ± 0.400 (50)	[0.722]	0.819 ± 0.530 (65)	[0.685]
t _{max} (h)	6.00 (0.50 , 9.98)		4.00 (1.00 , 24.00)		t _{max} (h)	10.00 (4.00 , 24.00)		3.02 (1.00 , 23.98)	
t _{1/2z} (h)	14.3 ± 10.0 (70)	[11.9]	65.8 ± 107 (162)	[41.1]	t _{1/2z} (h)	21.3 ± 15.9 (74)	[17.9]	35.0 ± 12.8 (36)	[33.3]
AUC _{0-τ} (h.ng/mL)	7.94 ± 3.99 (50)	[7.05]	8.36 ± 6.05 (72)	[6.77]	AUC _{0-τ} (h.ng/mL)	11.4 ± 5.95 (52)	[10.3]	12.1 ± 8.02 (67)	[10.1]
Ortho-hydroxy-atorvastatin									
PK Parameter	Morning		Evening		PK Parameter	Morning		Evening	
C _{max} (ng/mL)	6.49 ± 3.86 (60)	[5.70]	5.54 ± 2.72 (49)	[4.95]	C _{max} (ng/mL)	5.54 ± 2.07 (37)	[5.24]	7.87 ± 4.01 (51)	[6.98]
t _{max} (h)	3.00 (0.50 , 9.98)		4.00 (1.02 , 6.00)		t _{max} (h)	8.00 (4.00 , 10.03)		3.00 (1.00 , 6.00)	
t _{1/2z} (h)	7.50 ± 1.21 (16)	[7.41]	12.1 ± 3.43 (28)	[11.6]	t _{1/2z} (h)	7.63 ± 1.88 (25)	[7.43]	14.7 ± 7.68 (52)	[13.4]
AUC _{0-τ} (h.ng/mL)	57.4 ± 23.9 (42)	[53.6]	55.3 ± 26.5 (48)	[50.4]	AUC _{0-τ} (h.ng/mL)	69.9 ± 26.3 (38)	[66.2]	76.8 ± 40.6 (53)	[68.4]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} where values are Median (Min, Max)

[Source: Sponsor's report int10409, Tables15, 16, 20, 21, 24, 25 page 76, 79, 81]

Histogram plots for the distribution of t_{max} differences between dosing atorvastatin with or without lixisenatide are presented in [Figure 38](#) for the morning and evening dose of atorvastatin.

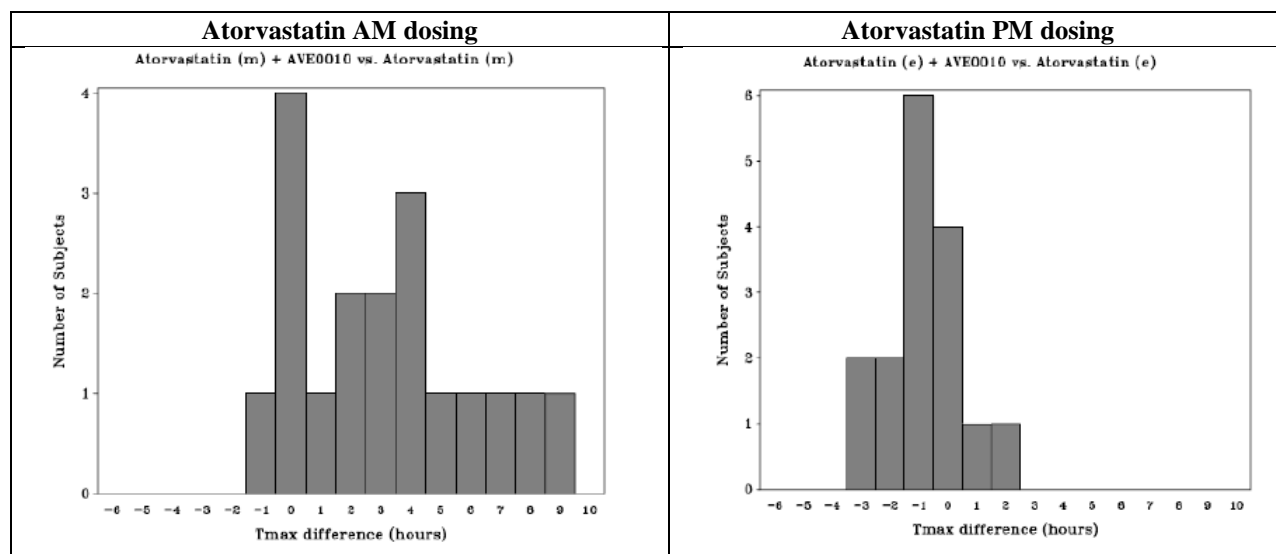


Figure 38 Histogram for the distribution of t_{max} differences between dosing atorvastatin with or without lixisenatide (morning dose- Group A; evening dose – Group B)

[Source: Sponsor’s report int10409, Figures 9,10 page 78]

As can be seen from [Table 42](#), there was an approximately 30% reduction in atorvastatin C_{max} when atorvastatin was administered alone in the evening compared to atorvastatin alone in the morning, and these findings are in agreement with reported values (“Plasma LIPITOR concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning”, Lipitor label approved on 10/31/2012 sourced from http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020702s062s063lbl.pdf). The steady-state C_{max} of atorvastatin was reduced by 31%, AUC was unaltered, and t_{max} was prolonged (with change in t_{max} ranging from -1 to 9 hours) when atorvastatin was administered in morning 1 hour after lixisenatide injection. However, when atorvastatin was administered in evening 12.5 hours following lixisenatide administration in the morning, C_{max} of atorvastatin was increased by 66%, AUC was increased by 27%, and t_{max} was unaltered (with change in t_{max} ranging from -3 to 2 hours).

There was no explanation for the increased atorvastatin exposure observed for the evening dose of atorvastatin together with lixisenatide compared to atorvastatin alone. Atorvastatin t_{max} for the evening dose was not affected, hence it is likely that lixisenatide induced effect on delayed gastric emptying did not last for 12.5 hours. Comparison of C_{max} and AUC values for atorvastatin when it was administered in the evening following lixisenatide morning administration, to atorvastatin administered alone in the morning showed a 25% increase in C_{max} and 18% increase in AUC for the evening administration.

Point estimates for the 2 main metabolites of atorvastatin indicated an increase of C_{max} and AUC in combination treatment with lixisenatide compared to atorvastatin alone. The increase was similar in the evening and morning dose groups, except for ortho-hydroxy-atorvastatin C_{max} in the morning dose group. The parallel increase of exposure for the metabolites and parent compound suggested that lixisenatide did not affect atorvastatin metabolism.

The statistical analysis of pharmacokinetic parameters is summarized in the [Table 43](#) below.

Table 43 Treatment ratio estimates of atorvastatin plus lixisenatide versus atorvastatin alone with 90% confidence intervals

AM dose (Group A) of atorvastatin for atorvastatin pharmacokinetics			
Parameter	Comparison	Estimate	90% CI
C _{max} (ng/mL)	Atorvastatin (m)+ AVE0010 vs. Atorvastatin(m)	0.69	(0.55 to 0.86)
AUC _{0_24} (ng.h/mL)	Atorvastatin (m)+ AVE0010 vs. Atorvastatin(m)	1.08	(0.99 to 1.18)
PK parameters are for Atorvastatin morning (m) P1: Atorvastatin 40mg QD morning P2: Atorvastatin 40mg QD morning + AVE0010 20µg QD			
PM dose (Group A) of atorvastatin for atorvastatin pharmacokinetics			
Parameter	Comparison	Estimate	90% CI
C _{max} (ng/mL)	Atorvastatin (e)+ AVE0010 vs. Atorvastatin(e)	1.66	(1.36 to 2.03)
AUC _{0_24} (ng.h/mL)	Atorvastatin (e)+ AVE0010 vs. Atorvastatin(e)	1.27	(1.18 to 1.36)
PK parameters are for Atorvastatin evening (e) P1: Atorvastatin 40mg QD evening P2: Atorvastatin 40mg QD evening + AVE0010 20µg QD			
Atorvastatin AM vs PM			
Parameter	Comparison	Estimate	90% CI
C _{max} (ng/mL)	Atorvastatin morning vs. Atorvastatin evening	1.43	(1.07 to 1.92)
AUC _{0_24} (ng.h/mL)	Atorvastatin morning vs. Atorvastatin evening	1.18	(0.91 to 1.52)
AM dose (Group A) of atorvastatin for p-OH-atorvastatin pharmacokinetics			
Parameter	Comparison	Estimate	90% CI
C _{max} (ng/mL)	Atorvastatin (m)+ AVE0010 vs. Atorvastatin(m)	1.44	(1.27 to 1.62)
AUC _{0_24} (ng.h/mL)	Atorvastatin (m)+ AVE0010 vs. Atorvastatin(m)	1.47	(1.32 to 1.63)
PK parameters are for Atorvastatin morning (m)			
PM dose (Group A) of atorvastatin for p-OH-atorvastatin pharmacokinetics			
Parameter	Comparison	Estimate	90% CI
C _{max} (ng/mL)	Atorvastatin (e)+ AVE0010 vs. Atorvastatin(e)	1.52	(1.32 to 1.75)
AUC _{0_24} (ng.h/mL)	Atorvastatin (e)+ AVE0010 vs. Atorvastatin(e)	1.48	(1.37 to 1.60)
PK parameters are for Atorvastatin evening (e)			
AM dose (Group A) of atorvastatin for o-OH-atorvastatin pharmacokinetics			
Parameter	Comparison	Estimate	90% CI
C _{max} (ng/mL)	Atorvastatin (m)+ AVE0010 vs. Atorvastatin(m)	0.92	(0.79 to 1.07)
AUC _{0_24} (ng.h/mL)	Atorvastatin (m)+ AVE0010 vs. Atorvastatin(m)	1.23	(1.14 to 1.33)
PK parameters are for Atorvastatin morning (m) P1: Atorvastatin 40mg QD morning P2: Atorvastatin 40mg QD morning + AVE0010 20µg QD			
PM dose (Group A) of atorvastatin for o-OH-atorvastatin pharmacokinetics			
Parameter	Comparison	Estimate	90% CI
C _{max} (ng/mL)	Atorvastatin (e)+ AVE0010 vs. Atorvastatin(e)	1.37	(1.16 to 1.61)
AUC _{0_24} (ng.h/mL)	Atorvastatin (e)+ AVE0010 vs. Atorvastatin(e)	1.31	(1.21 to 1.43)
PK parameters are for Atorvastatin evening (e) P1: Atorvastatin 40mg QD evening P2: Atorvastatin 40mg QD evening + AVE0010 20µg QD			

[Source: Sponsor's report int10409, Tables 17-19, 22, 23, 26, 27 pages 76-82]

Prolongation in t_{max} by up to 9 hours following AM dosing is not likely to affect the steady-state

concentrations of atorvastatin, but it may affect the time it takes to reach steady-state. For a chronically administered drug such as atorvastatin, total exposure at steady-state (AUC_{τ}) is the most important pharmacokinetic parameter. There is an 18% increase in AUC following evening administration of atorvastatin following lixisenatide morning administration, compared to atorvastatin administered alone in the morning. This increase in total exposure may not be clinically significant. In addition, safety of atorvastatin when given with lixisenatide is also addressed based on data from phase 3 trials. Based on a survey of common cardiovascular concomitant medications used in the completed Phase 3 placebo-controlled studies, sponsor reported that statins and statin combinations represented 38% of the medications. Overall, in the Phase 3 placebo-controlled studies, 1717 patients (lixisenatide: 1087/2869, 37.9%; placebo: 630/1639, 38.4%) were enrolled, who reported concomitant statin or statin combination use (*source: Integrated Summary of Safety, Table 26, page 109*). Patients with concomitant use of statins (or statin combinations) reported more treatment-emergent adverse events during the entire treatment period than patients with no concomitant statin use. However, this trend was observed in both the lixisenatide and placebo groups (85.3% in the lixisenatide group and 79.0% in the placebo group with statin use compared with 76.7% in the lixisenatide group and 65.2% in the placebo group without statin use) (*source: Integrated Summary of Safety, Appendix 1.2.2.12, Page 1062*). Neither myopathy nor increase in creatinine phosphokinase was reported in the Phase 3 trials.

Reviewer Comments:

Based on safety information from Phase 3 trials, and information garnered from approved label for atorvastatin that LDL-C reduction is the same regardless of the time of day of drug administration, no dose adjustment is recommended for atorvastatin. However, because of prolongation in time it may take to reach steady-state for atorvastatin, patients taking atorvastatin should be advised to take atorvastatin preferably 1 hour before lixisenatide administration.

2.5.2.2.4 Ramipril

This study assessed the effect of repeated subcutaneous doses of 20 μ g lixisenatide on the pharmacokinetic profile of ramipril and its active metabolite ramiprilat, and the pharmacodynamic response to ramipril in 30 healthy male and female subjects between 18 and 45 years of age.

This was a single-center, open-label, randomized, 2-treatment, 2-period, 2-sequence crossover study with a minimum washout period of 23 days (from last ramipril dosing day of the first period to first ramipril dosing day of the 2nd period). In treatment A, subjects received a daily dose of ramipril 5 mg for 6 days (Day 1 to Day 6). In treatment B, subjects received a run-in 10 μ g daily dose of lixisenatide for 7 days (Day 1 to Day 7) followed by a 20- μ g daily dose of lixisenatide for 7 days (Day 8 to Day 14) administered concomitantly with 6 daily doses of 5 mg ramipril on Day 9 to Day 14.

Mean plasma ramipril, ramiprilat and lixisenatide concentration-time profiles and ramiprilat trough concentrations separated by treatment are shown in [Figure 39](#).

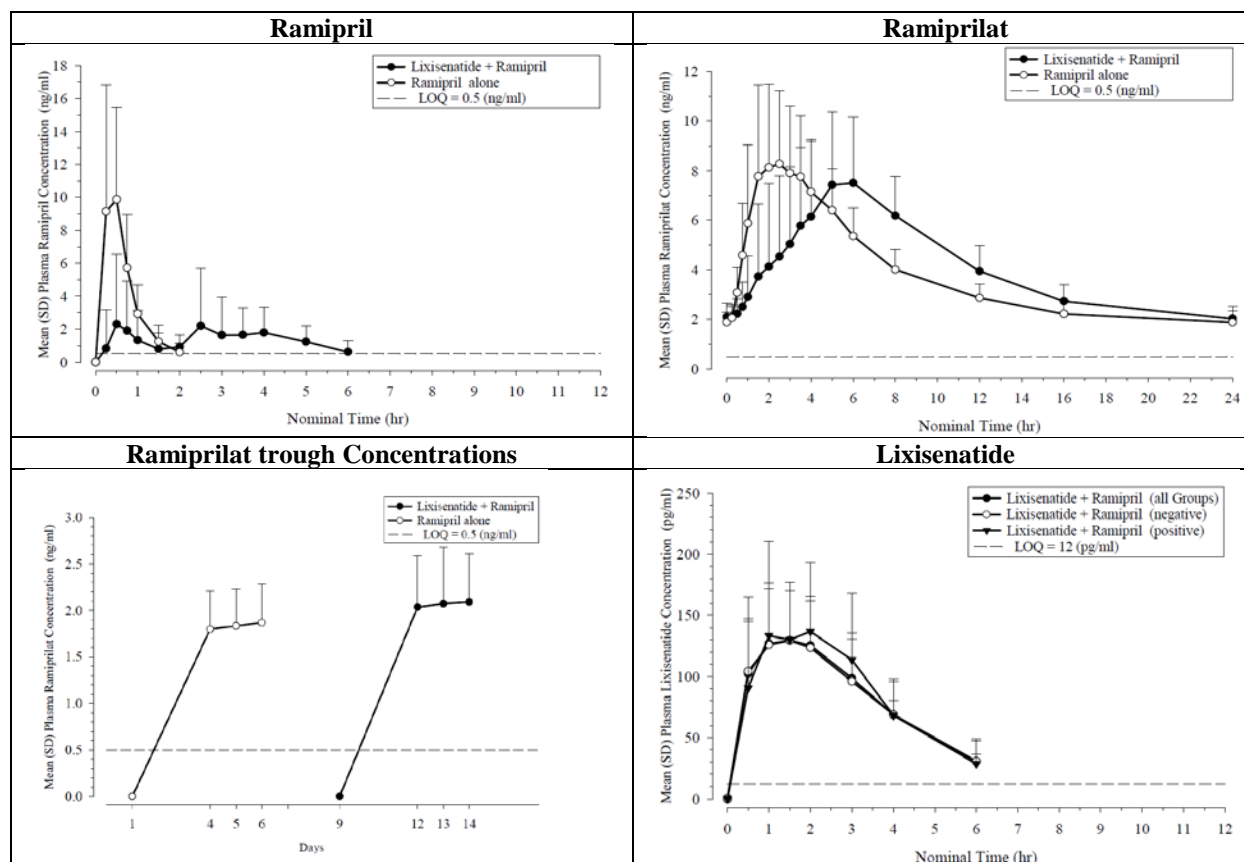


Figure 39 Mean plasma ramipril, ramiprilat and lixisenatide concentration-time profiles and ramiprilat trough concentrations

[Source: sponsor's study INT10782, Figures 2, 4, 6, 7, Pages 66-69]

The statistical analysis of pharmacokinetic parameters is summarized in the [Table 44](#) below.

Table 44 Treatment ratio estimates with 90% confidence intervals for ramipril and ramiprilat

Ramipril			
Parameter	Comparison	Estimate	90% CI
AUC ₀₋₂₄ (ng.h/mL)	Ramipril + lixisenatide vs. Ramipril	1.21	(1.06 to 1.39)
C _{max} (ng/mL)	Ramipril + lixisenatide vs. Ramipril	0.37	(0.29 to 0.46)
Ramiprilat			
Parameter	Comparison	Estimate	90% CI
AUC _{0-24h} (ng.h/mL)	Ramipril + lixisenatide vs. Ramipril	1.11	(1.06 to 1.16)
C _{max} (ng/mL)	Ramipril + lixisenatide vs. Ramipril	1.02	(0.92 to 1.14)

[Source: sponsor's study INT10782, Tables 22, 24, Pages 73, 76]

When ramipril was administered with breakfast 30 minutes post lixisenatide injection, the steady-state C_{max} of ramipril was reduced by 73% compared to ramipril administered alone. Steady-state AUC for ramipril was increased by 21%. T_{max} was prolonged from 0.5 hours with ramipril alone to 2.8 hours

following ramipril given 30 minutes post lixisenatide injection. For ramipril, the 90% CI for the ratio estimates (1.06-1.39) for AUC_{0-24} (equal to AUC_{τ}) was outside the upper bound of the reference interval of 0.80 – 1.25. For C_{max} , the 90% confidence intervals (0.29-0.46) were completely outside this range. Therefore a lack of interaction between ramipril and lixisenatide cannot be concluded.

For ramiprilat, the active moiety of ramipril, however, there was essentially no change in C_{max} (ratio 1.02) and AUC (ratio 1.11) between ramipril+lixisenatide and ramipril treatments. T_{max} for ramiprilat, however, was prolonged from 2.5 hours with ramipril alone to 5.0 hours following ramipril given 30 minutes post lixisenatide injection. Mean trough concentrations of ramiprilat were similar between the two treatments (1.85 ng/mL following ramipril alone vs. 1.94 ng/mL following ramipril+lixisenatide). The 90% CIs for the ratio estimates of lixisenatide + ramipril versus ramipril alone were entirely within the [0.80 – 1.25] boundaries for C_{max} and AUC_{0-24h} (equal to AUC_{τ}) of ramipril's active metabolite ramiprilat, indicating a lack of interaction of repeated doses of lixisenatide at a dose of 20 μ g on the repeated-dose pharmacokinetics of ramiprilat after a 5-mg dose of ramipril at steady state.

Reviewer Comments:

Ramipril is almost completely metabolized in the body to ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril. Since the total exposure and trough concentrations of ramiprilat did not change following administration with lixisenatide compared to lixisenatide alone, no dose adjustment for ramipril is suggested when co administered with lixisenatide.

2.5.2.2.5 Digoxin

This study assessed the effect of repeated subcutaneous (SC) doses of 20 μ g lixisenatide on the pharmacokinetic (PK) profile of digoxin in 24 healthy male and female subjects between 18 and 45 years of age inclusive.

This was a single-center, open-label, randomized, 2-sequence, 2-period, 2-treatment crossover study with a minimum 14 days washout period between the 2 administration periods.

There were 2 treatment arms in the study. In Treatment A, digoxin 0.25 mg BID was administered on Day 1 followed by 0.25 mg QD for 6 days (Days 2-7). In Treatment B, lixisenatide was dosed with a starting dose of 10 μ g QD for 7 days (Day 1 to Day 7) followed by an up titration to 20 μ g QD for 10 days (Day 8 to Day 17). Concomitantly to lixisenatide, digoxin was administered 0.25 mg BID for 1 day (in the morning and evening of Day 11), followed by digoxin 0.25 mg QD for 6 days (in the morning of Days 12-17). The wash-out between the 2 treatment periods was at least 14 days.

Mean plasma digoxin concentration-time profiles separately by treatment are shown in [Figure 40](#).

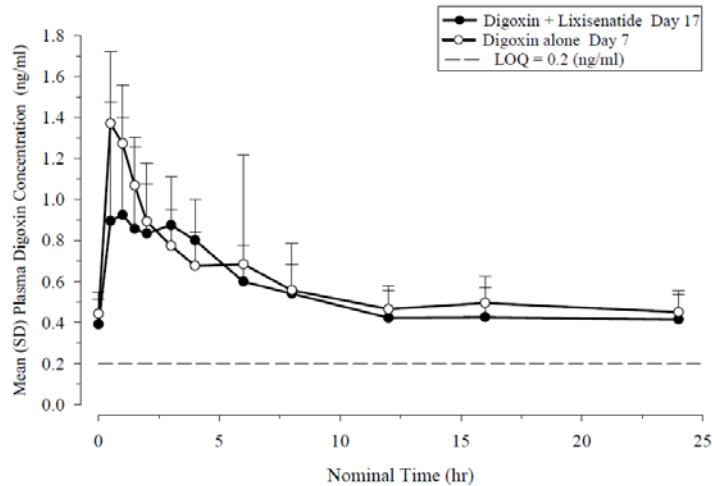


Figure 40 Mean (+SD) digoxin plasma concentrations

[Source: sponsor's study INT10783, Figure 2, Page 68]

Statistical analysis of digoxin pharmacokinetic parameters is summarized in the [Table 45](#) below.

Table 45 Treatment ratio estimates of digoxin plus lixisenatide versus digoxin alone with 90% CI

Parameter	Group / Comparison	Estimate	90% CI
C_{max} (ng/mL)	Digoxin+Lixisenatide vs Digoxin	0.74	(0.64 to 0.86)
AUC_{τ} (ng.h/mL)	Digoxin+Lixisenatide vs Digoxin	0.94	(0.87 to 1.01)

[Source: sponsor's study INT10783, Table 22, Page 73]

When digoxin was administered with breakfast 30 minutes post lixisenatide injection, the steady-state C_{max} of digoxin was reduced by 26% compared to digoxin administered alone. Steady-state AUC for digoxin remained unchanged between the treatments. T_{max} was prolonged from 0.5 hours with digoxin alone to 2 hours following digoxin given 30 minutes post lixisenatide injection.

The 90% CI for AUC_{τ} of digoxin was entirely within the protocol-specified boundaries [80, 125%], following repeated doses of 20 μ g lixisenatide on repeated dose of digoxin 0.25 mg, indicating that lixisenatide did not affect the overall exposure of warfarin when administered concomitantly.

The lower bound for the 90% CI for digoxin C_{max} was however, outside the protocol-specified boundaries (geometric mean of the ratio estimate of digoxin plus lixisenatide versus digoxin alone 0.74, with 90% CI of 0.64-0.86), demonstrating an influence of lixisenatide on the rate of digoxin exposure.

The shift of median T_{max} values for digoxin from 0.5 hour when digoxin was administered alone to 2 hours when administered concomitantly with lixisenatide was possibly due to the known delaying effect of lixisenatide on gastric emptying.

Reviewer Comments:

Due to the lixisenatide induced delay in time to peak digoxin concentrations, careful monitoring of digoxin levels are recommended. The health care provider should be cautioned to follow instructions in the product monograph for digoxin for appropriate dose adjustment, if necessary when administering with lixisenatide.

2.5.2.2.6 Oral Contraceptives

This study assessed the effect of a 10 µg injection of lixisenatide on the pharmacokinetic parameters of a single dose of oral contraceptive (OC) at various time points in relation to a 10 µg subcutaneous (SC) injection of lixisenatide in healthy post-menopausal female subjects.

This was a single-center, single-blind, placebo-controlled, randomized, 5-treatment, 5-period crossover study in 25 healthy post-menopausal female subjects, aged between 40 and 65 years, with body weight between 50 and 80 kg and a body mass index (BMI) between 18 and 28 kg/m², and not using hormonal therapy.

The subjects received 10 µg (0.1 mL) lixisenatide once daily (QD) on Day 1 and/or Day 2, depending on treatment regimen via SC administration at 8 PM on Day 1 and at 8 AM on Day 2 with concomitant treatment of 1 tablet of an oral contraceptive (OC) (Minidril, containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel). The reference therapy was a matching placebo administered SC at 8 PM on Day 1 and at 8 AM on Day 2 with concomitant treatment 1 tablet of OC. Five different treatment plans were conducted as shown in [Table 46](#) below. The single dose OC was administered at -1 hour relative to placebo injection (treatment A) on Day 2, -1 hour relative to lixisenatide injection (Treatment C) on Day 2, + 1 hour relative to lixisenatide injection (treatment D) on Day 2, + 4 hours (treatment E) relative to lixisenatide injection on Day 2 and + 11 hours (treatment B) relative to lixisenatide injection on Day 1.

Table 46 Treatment regimen for lixisenatide and oral contraceptive

Treatments	Day 1		Day 2		
	8 PM	7 AM	8 AM	9 AM	12 noon
A	AVE0010 placebo- injection	OC	AVE0010 placebo- injection		
B^a	AVE0010 injection	OC	AVE0010 placebo- injection		
C^b	AVE0010 injection	OC	AVE0010 injection		
D	AVE0010 placebo- injection		AVE0010 injection	OC	
E	AVE0010 placebo- injection		AVE0010 injection		OC

^a designed to mimic a QD regimen of AVE0010 administration

^b designed to mimic a BID regimen of AVE0010 administration

OC = oral contraceptive (Minidril)

[Source: sponsor's study INT6052, Table 1, Page 18]

Mean plasma concentrations of ethinylestradiol and levonorgestrel obtained after administration of the oral contraceptive co-administered with placebo (treatment A) or 11 hours after lixisenatide (treatment B), 1 hour before lixisenatide (treatment C), 1 hour after lixisenatide (treatment D) and 4 hours after lixisenatide (treatment E) are presented in [Figure 41](#).

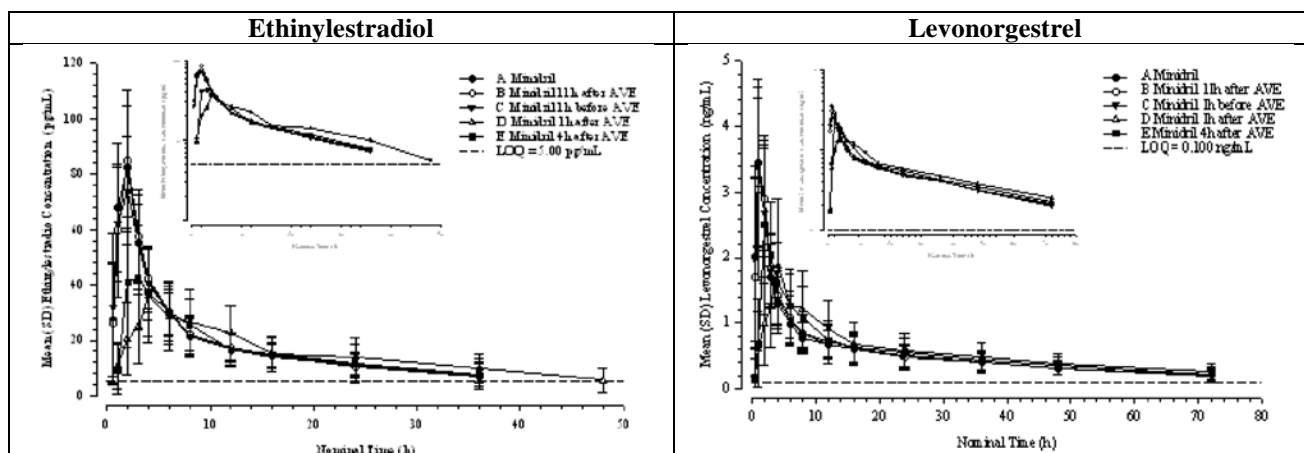


Figure 41 Mean ($\pm$ SD) ethinylestradiol and levonorgestrel plasma concentrations observed after single administration of oral contraceptive co-administered with placebo or lixisenatide (administered via SC injection), linear and log scale (embedded graph)

[Source: sponsor’s study INT6052, Figures 1 and 2, Page 67]

Ethinylestradiol and levonorgestrel pharmacokinetic parameter ratio estimates with 90% CIs for treatment differences are reported in [Table 47](#).

Table 47 Ratio estimates and corresponding 90% CIs for treatment comparisons

Oral contraceptive	Parameter	Treatment comparison	Ratio	
			Estimate	90% CI
Ethinylestradiol	C _{max}	B vs. A	0.99	(0.90, 1.09)
		C vs. A	0.93	(0.84, 1.02)
		D vs. A	0.48	(0.43, 0.53)
		E vs. A	0.61	(0.56, 0.68)
		LOQ = 5.00 ppb/L		
	AUC _{last}	B vs. A	1.00	(0.89, 1.13)
		C vs. A	1.01	(0.90, 1.14)
		D vs. A	0.96	(0.85, 1.09)
		E vs. A	0.95	(0.84, 1.08)
AUC	B vs. A	1.03	(0.97, 1.09)	
	C vs. A	1.00	(0.94, 1.06)	
	D vs. A	1.06	(1.00, 1.12)	
	E vs. A	0.96	(0.91, 1.02)	
Levonorgestrel	C _{max}	B vs. A	1.00	(0.88, 1.15)
		C vs. A	1.01	(0.89, 1.16)
		D vs. A	0.54	(0.48, 0.62)
		E vs. A	0.80	(0.70, 0.92)
		LOQ = 0.100 ng/mL		
	AUC _{last}	B vs. A	1.03	(0.87, 1.22)
		C vs. A	1.01	(0.85, 1.20)
		D vs. A	1.00	(0.84, 1.19)
		E vs. A	1.09	(0.92, 1.30)
AUC	B vs. A	1.02	(0.94, 1.11)	
	C vs. A	0.99	(0.92, 1.08)	
	D vs. A	1.20	(1.10, 1.31)	
	E vs. A	1.14	(1.05, 1.24)	

Treatment A - single Minidril oral administration co-administered with placebo;
 Treatment B - single Minidril oral administration co-administered 11 hours after AVE0010;
 Treatment C - single Minidril oral administration co-administered 1 hour before AVE0010;
 Treatment D - single Minidril oral administration co-administered 1 hour after AVE0010;
 Treatment E - single Minidril oral administration co-administered 4 hours after AVE0010.

[Source: sponsor’s study INT6052, Table 27, Page 72]

Statistical analysis performed on ethinylestradiol pharmacokinetic parameters showed the following:

- C_{max} of ethinylestradiol reduced 52% when oral contraceptive was administered 1 hour (treatment D) compared to placebo (treatment A). When the OC was administered 4 hours (treatment E) after lixisenatide injections, the reduction in ethinylestradiol C_{max} was 39% compared to OC administration with placebo injection (treatment A). The ratio estimate values

were 0.48 (D versus A) and 0.61 (E versus A) with 90% CIs outside the limits [0.80; 1.25] ([Table 47](#)).

- $C_{\max}$ of ethinylestradiol when oral contraceptive was administered 11 hours after (treatment B) or 1 hour before lixisenatide injection (treatment C) was similar to that observed after oral contraceptive with placebo injection (treatment A). The ratio estimates were 0.99 (B versus A) and 0.93 (C versus A) with 90% CI interval within the limits [0.80; 1.25] indicating that lixisenatide injection does not change $C_{\max}$ of ethinylestradiol when oral contraceptive is administered 11 hours after (treatment B) or 1 hour before lixisenatide injection (treatment C) ([Table 47](#)).
- AUC_{last} and AUC of ethinylestradiol after co-administration of oral contraceptive with lixisenatide, independent of the relative time point between both medications, were similar to those observed after administration of oral contraceptive with placebo. The ratio estimate values were between 0.95 and 1.01 for AUC_{last} and 0.96 and 1.06 for AUC. Their 90% CIs were within the interval [0.80; 1.25] indicating that lixisenatide injection does not affect AUC_{last} and AUC of ethinylestradiol ([Table 47](#)).
- The median $t_{\max}$ of ethinylestradiol was increased from 2 hours to 4 or 3 hours when oral contraceptive was administered 1 hour (treatment D) or 4 hours (treatment E) after lixisenatide injection compared to oral contraceptive with placebo injection (treatment A). However, no effect on the median $t_{\max}$ was observed when oral contraceptive was administered 1 hour before (treatment C) or 11 hours (treatment B) after lixisenatide injection.

Similarly, statistical analysis performed on levonorgestrel pharmacokinetic parameters showed the following:

- $C_{\max}$ of levonorgestrel reduced by 46% when oral contraceptive was administered 1 hour (treatment D) after lixisenatide injection. When the OC was administered 4 hours (treatment E) after lixisenatide injection, the reduction in $C_{\max}$ of levonorgestrel was 20% compared to OC administration with a placebo injection (treatment A). The ratio estimate values were 0.54 (D versus A) and 0.80 (E versus A) with lower limits of 90% CIs (0.48 and 0.70, respectively) smaller than 0.8 indicating a decrease in $C_{\max}$ of levonorgestrel when oral contraceptive was administered 1 hour (treatment D) or 4 hours (treatment E) after lixisenatide injection ([Table 47](#)).
- $C_{\max}$ of levonorgestrel when oral contraceptive was administered 11 hours after (treatment B) or 1 hour before lixisenatide injection (treatment C) was similar to that observed after oral contraceptive with placebo injection (treatment A). The ratio estimates were 1.00 (B versus A) and 1.01 (C versus A) with 90% CI interval within the limits [0.80; 1.25] indicating that lixisenatide injection does not change $C_{\max}$ of ethinylestradiol when oral contraceptive is administered 11 hours after (treatment B) or 1 hour before lixisenatide injection (treatment C) ([Table 47](#)).
- AUC_{last} and AUC of levonorgestrel after co-administration of oral contraceptive with lixisenatide, independent of the relative time point between both medications, were similar to those observed after administration of oral contraceptive with placebo. The ratio estimate values were between 1.00 and 1.09 for AUC_{last} and 0.99 and 1.20 for AUC. Their lower limits of 90% CIs were greater than 0.8 indicating that lixisenatide injection does not affect AUC_{last} and AUC of ethinylestradiol ([Table 47](#)).
- The median $t_{\max}$ of levonorgestrel was increased from 1 hour to 4 or 2 hours when oral contraceptive was administered 1 hour (treatment D) or 4 hours (treatment E) after lixisenatide injection compared to oral contraceptive with placebo injection (treatment A). However, no effect on the median $t_{\max}$ was observed when oral contraceptive was administered 1 hour before (treatment C) or 11 hours after lixisenatide injection (treatment B).

Reviewer Comments:

The clinical implications of reduced peak exposure of ethinylestradiol and levonorgestrel when the oral contraceptive was administered 1 hour or 4 hours after lixisenatide injection, is unknown. It is quite possible that oral contraceptives depend on threshold concentrations for efficacy. Therefore, patients should be advised to take oral contraceptives at least 1 hour before lixisenatide administration or 11 hours after the morning dose of lixisenatide.

2.6 General Biopharmaceutics

2.6.1 What is absolute bioavailability and disposition of Lixisenatide?

The sponsor reported that one relative bioavailability study in non-diabetic subjects (study BDR12546) included an IV treatment arm to assess the absolute bioavailability of lixisenatide. They report that the absolute bioavailability was determined for the SC administration using the reference formulation with a lixisenatide concentration of 100 µg/mL, which was also used for the IV injection. The absolute bioavailability was reported to be 32%, for both AUC_{last} and AUC, with a 90% CI range of 24% to 42%. However, the sponsor only provided a protocol for this study, and in absence of a full study report, these reported results cannot be verified.

2.6.2 Is bioequivalence established between the to-be-marketed formulation and the Phase 3 trial formulation and how does it relate to the overall product development?

Proposed commercial formulation is the same as the one used in Phase I, II and III studies. An overview on the formulation history is shown in [Figure 42](#).



Figure 42 Formulation history of lixisenatide parenteral formulations

[Source: sponsor's Quality overall summary, module 2.3.P, Figure 2, Page 10]

2.6.3 Are the two to-be-marketed strengths bioequivalent?

The sponsor conducted a study to determine the bioequivalence of 2 different formulations with different lixisenatide concentrations (50 µg vs. 100 µg lixisenatide/ mL of lixisenatide) in 90 healthy male and female subjects, aged 18 to 45 years.

The test product, lixisenatide 50 µg/mL solution for injection was available in a 3-mL (b) (4) cartridge. A dose of 10 µg (0.2 mL of a 50 µg/mL solution) was used in the study. The reference product, lixisenatide 100 µg/mL solution for injection was also available in a 3-mL (b) (4) cartridge. A dose of 10 µg (0.1 mL of 100 µg/mL solution) was used in the study.

The study design was a single-center, open-label, randomized, single-dose, 3-sequence, 3-period replicate, 2-treatment crossover study. Healthy subjects, stratified by sex, were randomly allocated to 1 of 3 treatment sequences on Day 1 of Period 1 to receive a single dose of 10 µg lixisenatide in 1 of 2

concentrations, 50 µg/mL or 100 µg/mL, in each period ([Table 48](#)), with 2 replications of the 100 µg/mL formulation (reference). Doses were separated by a washout period of 48 to 96 hours.

Table 48 Treatment sequences for the bioequivalence study

Sequence	Treatment Period		
	1	2	3
1	Reference	Reference	Test
2	Test	Reference	Reference
3	Reference	Test	Reference

Test = test formulation = 10 µg lixisenatide at a concentration of 50 µg/mL

Reference = Reference formulation = 10 µg lixisenatide at a concentration of 100 µg/mL

[Source: sponsor's study BEQ11094, Table 1, Page 16]

Mean (SD) plasma lixisenatide concentration-time profiles for the test and the 2 reference treatments are shown in [Figure 43](#).

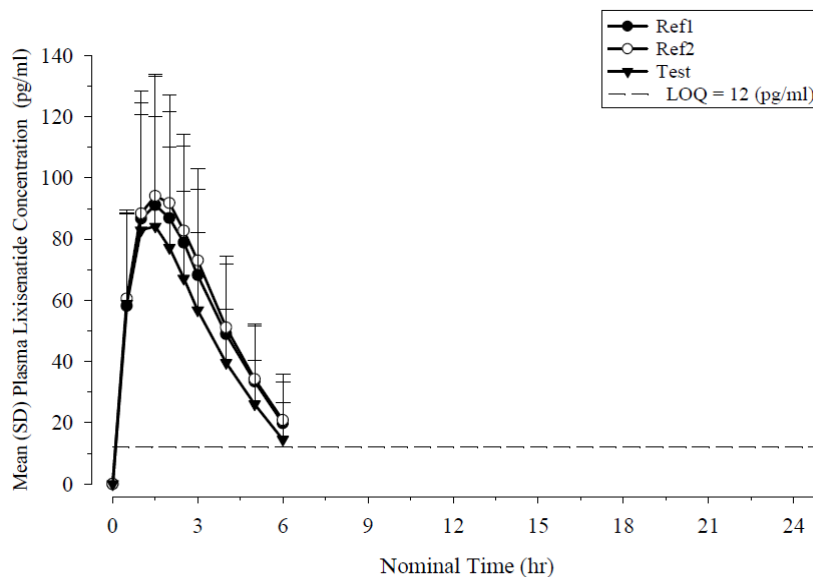


Figure 43 Mean (+ SD) lixisenatide plasma concentrations

[Source: sponsor's study BEQ11094, Figure 1, Page 54]

Lixisenatide pharmacokinetic parameter ratio estimates with 90% CIs for treatment differences are reported in [Table 49](#).

Table 49 Relative bioavailability analysis of lixisenatide test formulation versus lixisenatide reference formulation with 90% confidence interval

Parameter	Comparison	Estimate	90% CI
C_{max}	Test vs. Reference	0.89	(0.84 to 0.94)
AUC_{last}	Test vs. Reference	0.83	(0.78 to 0.89)
AUC	Test vs. Reference	0.86	(0.81 to 0.92)

AUC values with more than 20% extrapolation rate were not taken into account.
[Source: sponsor's study BEQ11094, Table 17, Page 59]

The 90% CI for C_{max} and AUC of lixisenatide were within the protocol-specified boundaries [80, 125%], demonstrating bioequivalence for these parameters. However, for the parameter AUC_{last} , the lower bound of the 90% CI (0.78-0.89) was outside the protocol-specified boundaries [80, 125%]. The geometric mean of the ratio estimate was 0.83.

The within-subject variability was about 27% for AUC and AUC_{last} and 22% for C_{max} ; since the estimated within-subject standard deviation for the reference formulation (σ_{wR}) was < 0.30 for any log-transformed parameter, the scaled average bioequivalence (SABE) analysis described in Haidar² was not applicable. Hence, the sponsor conducted the standard average bioequivalence (ABE) analysis.

Reviewer Comment:

Based on the bioequivalence for the parameters AUC and C_{max} , the sponsor demonstrated that the 100 µg/mL and the 50 µg/mL formulations of lixisenatide were bioequivalent. For AUC_{last} the point estimate was within the bioequivalence interval but the lower limit of the confidence interval fell just below the bioequivalence limit.

2.7 Analytical

2.7.1 Is the analytical method for Lixisenatide appropriately validated?

The lixisenatide assay was validated for analyzing lixisenatide in plasma and serum samples in terms of recovery, linearity, accuracy, precision and sensitivity.

The assay to detect lixisenatide employed the quantitative double antibody sandwich enzyme immunoassay technique ([Figure 44](#)).

² Haidar SH et. al. Bioequivalence approaches for highly variable drugs and drug products. *Pharm Research*, 25(1): 237-241, 2008.

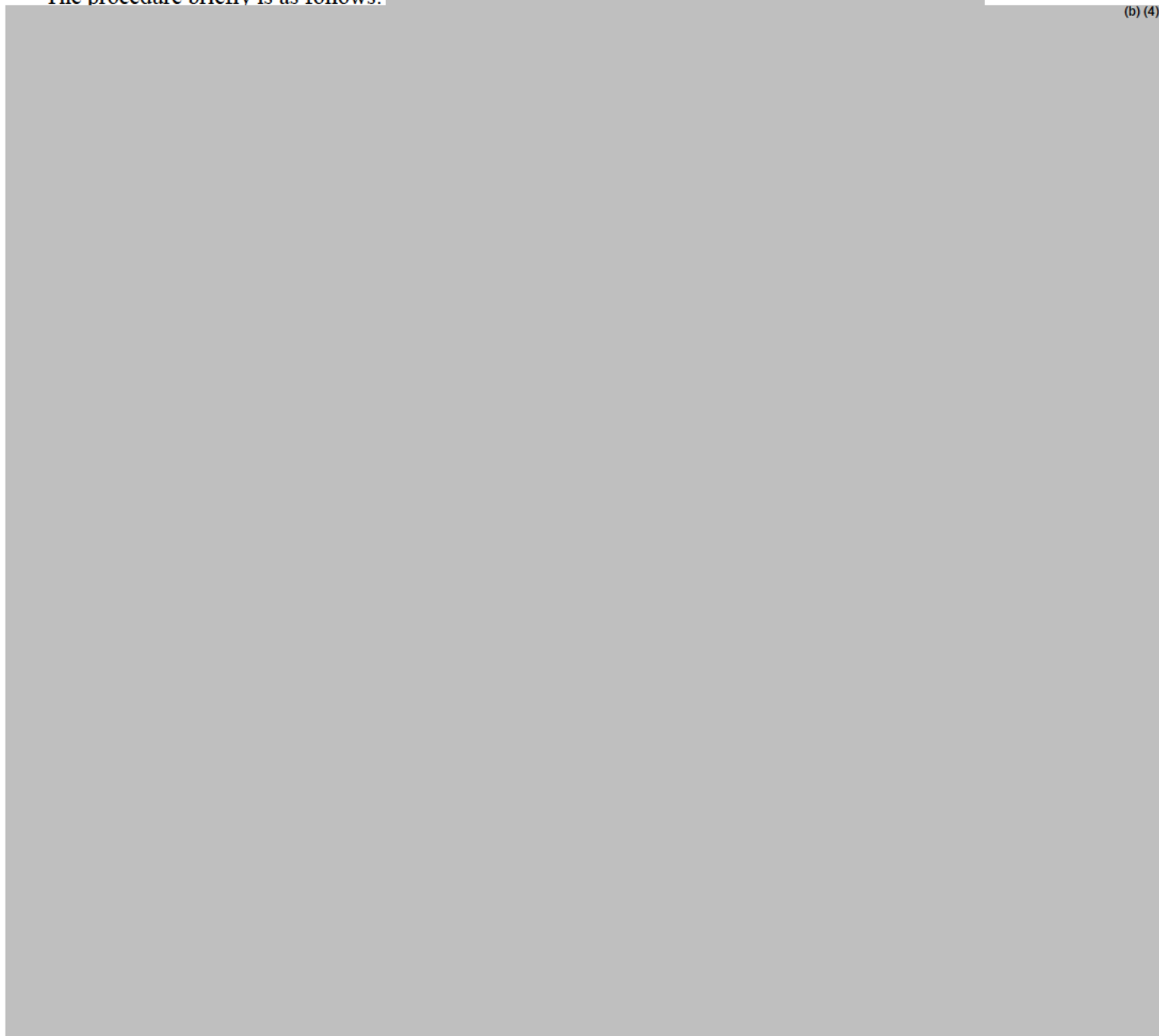


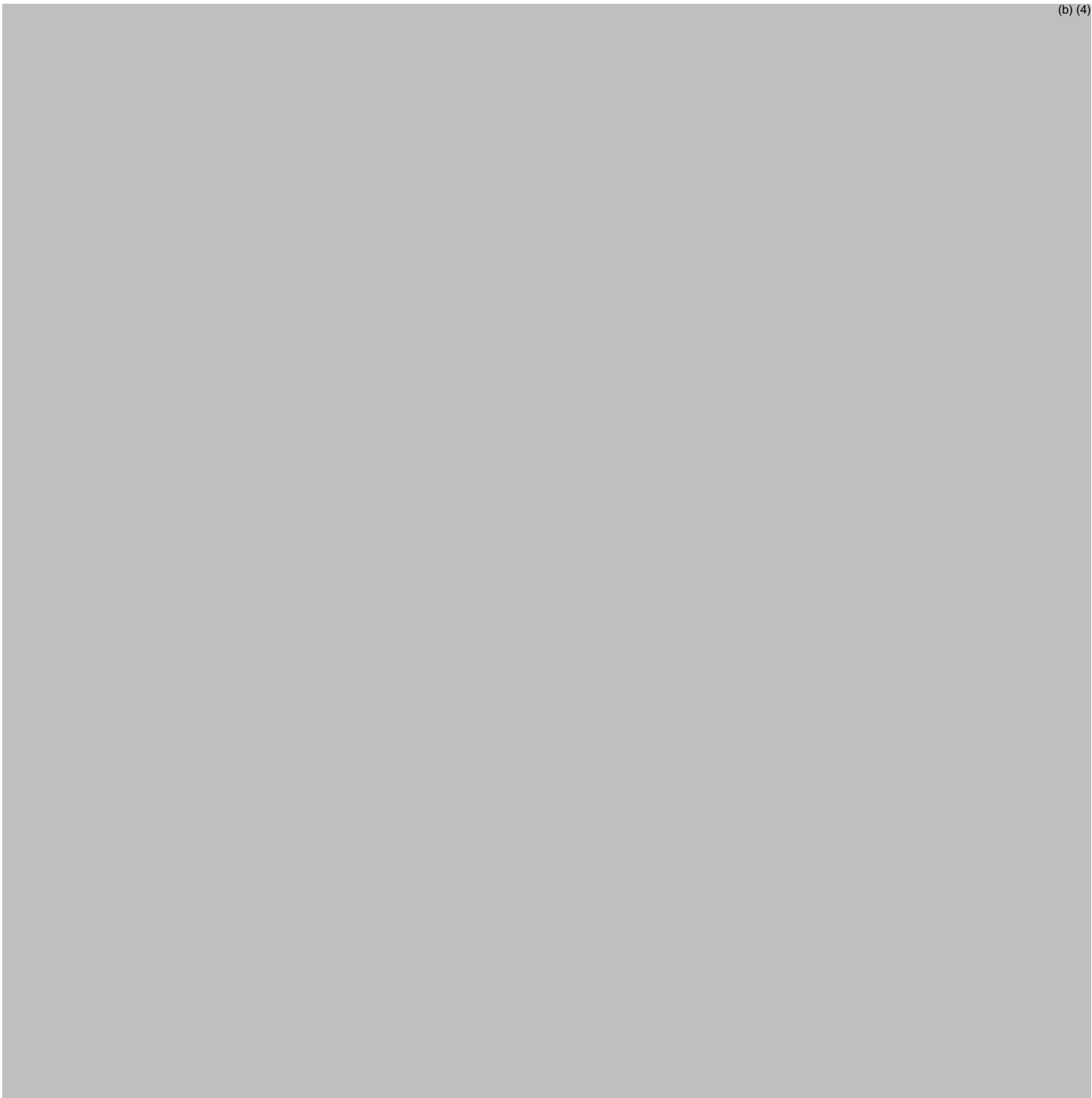
Figure 44 Schematic for Lixisenatide enzyme immunoassay

The procedure briefly is as follows:

(b) (4)

(b) (4)





A summary of key descriptive parameters for lixisenatide bioanalytical assays used in clinical studies is listed in [Table 50](#).

Table 50 Summary of key descriptive parameters for lixisenatide bioanalytical assays used in clinical studies

Method [Report Location]	Analyte	Type of method	Matrix (anti-coagulant)	Working range [pg/mL]	Coefficient of variation (%)						Clinical studies
					Inter-assay variability		Intra-assay variability		Inaccuracy		
					At LLOQ	At ULOQ	At LLOQ	At ULOQ	At LLOQ	At ULOQ	
F2005KIN0016 (AA23681) 5.3.1.4 [F2005KIN0016 (AA23681)] and [F2005KIN0016- amend01] and supportive information [F2005KIN0242]	Lixisenatide (unbound)	Double- antibody sandwich ELISA	Plasma (EDTA) without anti- lixisenatide antibodies	10-160	11.4	8.3	11.1	5.6	3	17	ACT6011
F2005KIN0133 (AA26641) (first generation assay) 5.3.1.4 [F2005KIN0133] and [F2005KIN0133- amend01]	Lixisenatide (total)	Double- antibody sandwich ELISA	Plasma (EDTA) in absence of anti-lixisenatide antibodies Plasma (EDTA) in presence of anti-lixisenatide antibodies	20-320 20-320	≤30 ≤30	≤25 ≤25	≤30 ≤30	≤25 ≤25	65-135 60-140	70-130 60-140	ACT6011 INT6052 INT6863
DOH0498 (EN_E01) (second generation assay) 5.3.1.4 [DOH0498-drug- assay]	Lixisenatide (total)	Double- antibody sandwich ELISA	Plasma (EDTA) with and without anti-lixisenatide antibodies	8.8-223	≤25	≤25	≤25	≤25	75-125	75-125	POP6053

Method [Report Location]	Analyte	Type of method	Matrix (anti-coagulant)	Working range [pg/mL]	Coefficient of variation (%)						Clinical studies
					Inter-assay variability		Intra-assay variability		Inaccuracy		
					At LLOQ	At ULOQ	At LLOQ	At ULOQ	At LLOQ	At ULOQ	
DOH0498 (AA43648) (third generation assay) 5.3.1.4 [DOH0498] and supportive information [DOH0498- Bridging] (EN_E02), [DOH0498- Bridging- Amend01] (EN_E02A01), and [DOH0498- Bridging- Amend02] (EN- A02)	Lixisenatide (total)	Double- antibody sandwich ELISA	Plasma (EDTA) with and without anti-lixisenatide antibodies	12-250	8.2	3.6	4.5	2.6	5.7	13.8	BDR6864 BEQ11094 DRI6012 EFC6014 EFC6015 EFC6016 EFC6017 EFC6018 EFC10743 EFC10780 EFC10781 EFC10887 EFC11321 INT10408 INT10409 INT10782 INT10783 LTS10888 PDY6797 PDY10433 PDY11431 PDY11824 PDY11941 POP11320 POP11814 TDR11215 TES6865 TES11807

Method [Report Location]	Analyte	Type of method	Matrix (anti-coagulant)	Working range [pg/mL]	Coefficient of variation (%)						Clinical studies
					Inter-assay variability		Intra-assay variability		Inaccuracy		
					At LLOQ	At ULOQ	At LLOQ	At ULOQ	At LLOQ	At ULOQ	
DOH0499 (CIR070128.01- 04) 5.3.1.4 [DOH0499]	Lixisenatide (biologic- ally active)	Cellular potency assay	Plasma (EDTA) with anti- lixisenatide antibodies	40-600	<20	<20	<20	<20	<20	<20	TDR11215 EFC6014 EFC6015 EFC6016 EFC6017 EFC6018 EFC10743 EFC10780 EFC10781 EFC10887 EFC11319 EFC11321 LTS10888

EDTA = ethylenediaminetetraacetic acid; ELISA = enzyme-linked immunosorbent assay; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification

2.8 Addendum

Information from four (4) new clinical pharmacology studies were available in the re-submission of Lixisenatide NDA (208471).

Bioavailability of a single 20 µg dose of lixisenatide from solutions of 200 µg/mL or 400 µg/mL compared with 100 µg/mL, and the absolute bioavailability of a 5 µg dose of lixisenatide from a 100 µg/mL solution was evaluated in study BDR12546.

The dose-response relationship of different doses of lixisenatide (2.5, 5, 10, and 20 µg) on glucose profiles and gastric emptying in healthy subjects was evaluated in study PDY12545.

The effect of lixisenatide doses of 5 µg and 10 µg on postprandial plasma glucose in pediatric (10 - 17 years old) and adult patients with type 2 diabetes was evaluated in study PKD11475.

The effect of repeated doses of lixisenatide 20 µg QD on postprandial plasma glucose compared to liraglutide 1.2 mg QD or 1.8 mg QD was evaluated in study PDY12625.

Findings from these 4 studies are discussed in this addendum.

2.8.1 Absolute and Relative Bioavailability of Lixisenatide (Study BDR12546)

The relative bioavailability of a subcutaneous (SC) injection of 20 µg lixisenatide using concentrations of 200 and 400 µg/mL compared with 100 µg/mL was evaluated in study BDR12546.

In this study, Lixisenatide solutions for injection were supplied in 3 dosage strengths: 100, 200, and 400 µg/mL. The doses evaluated were 20 µg for subcutaneous injection and 5 µg for IV infusion. The reference treatment (A) was a 200 µL subcutaneous injection of a 100 µg/mL solution for injection. The two test treatments were: treatment B, available as a 100 µL subcutaneous injection of a 200 µg/mL solution for injection (Test 1), and treatment C, available as a 50 µL subcutaneous injection of a 400 µg/mL solution for injection (Test 2). The intravenous administration (treatment D) was a 30 seconds IV infusion of 50 µL of the 100 µg/mL solution for injection.

Plasma lixisenatide concentration time profiles following the four treatments are shown in [Figure 45](#) below:

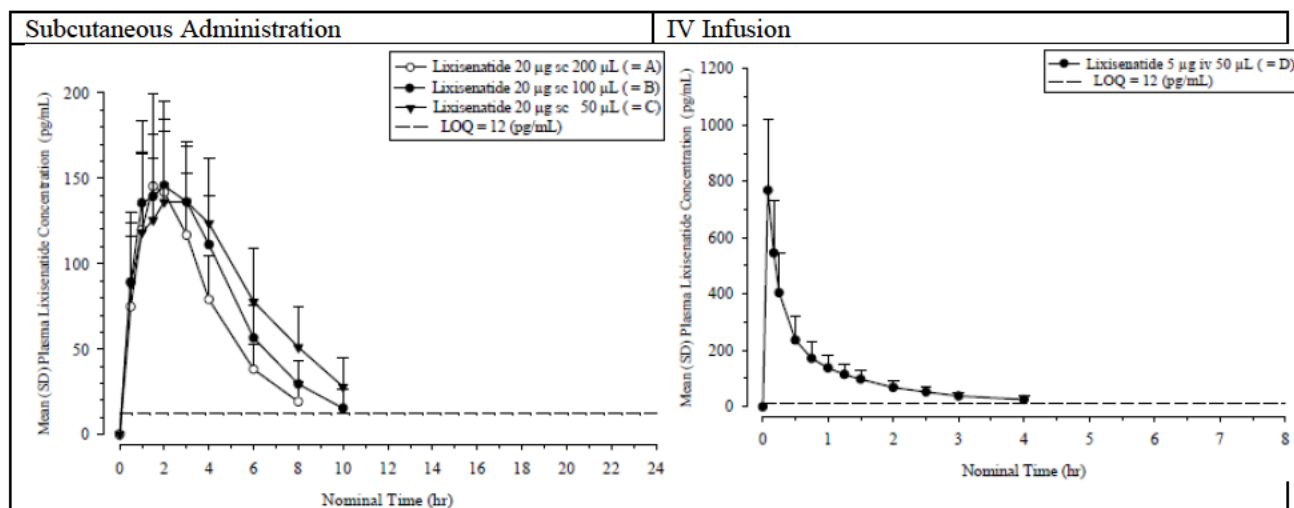


Figure 45: Mean (+SD) lixisenatide plasma concentrations after IV infusion and SC dosing

Source eCTD module 5.3.1.2, Study BDR12546, Figure 6, page 64 and Figure 8 page 65.

The absolute bioavailability of the SC administration of the 100 µg/mL formulation was 32% for total lixisenatide.

As the lixisenatide concentration in the formulation increased (and thus decreasing volume of injection), the relative bioavailability for AUC_{last} and AUC also increased. Compared to treatment A (20 µg, 200 µL of 100 µg/mL solution) there was an approximate 30% increase in the AUC values for lixisenatide following treatment B (20 µg, 100 µL of 200 µg/mL). Compared to treatment A (20 µg, 200 µL of 100 µg/mL solution) there was an approximate 45-50% increase in the AUC values for lixisenatide following treatment C (20 µg, 50 µL of 400 µg/mL) ([Table 51](#)). The 90% CI for these comparisons were outside the bioequivalence range. For the parameter C_{max} , however, the 2 treatments were still within the bioequivalence-range of 80% to 125% ([Table 52](#)).

Table 51: Pharmacokinetic data for lixisenatide (SC dosing) – ADA negative

Mean ± SD (Geometric Mean) [CV%]	Total Lixisenatide in Plasma		
	Lixisenatide 20 µg SC 200 µL (A)	Lixisenatide 20 µg SC 100 µL (B)	Lixisenatide 20 µg SC 50 µL (C)
N	14	14	13
C_{max} (pg/mL)	151 ± 52.7 (143) [34.9]	155 ± 41.8 (149) [27.0]	145 ± 41.3 (139) [28.5]
t_{max} ^a (h)	1.79 (1.00 - 3.00)	2.00 (1.00 - 3.00)	2.00 (1.02 - 4.00)
AUC_{last} (pg·h/mL)	619 ± 203 (584) [32.8]	777 ± 201 (749) [25.9]	860 ± 261 (821) [30.3]
AUC (pg·h/mL)	673 ± 212 (638) [31.5]	843 ± 216 (814) [25.7]	946 ± 298 (902) [31.5] b
$t_{1/2z}$ (h)	2.01 ± 0.488 (1.96) [24.3]	2.22 ± 0.461 (2.18) [20.7]	2.85 ± 0.726 (2.76) [25.5]

^a Median (Min - Max)

^b n=12, Subject 826 001 009 not included in calculation of summary statistics

Profile of Subject 826001003 was excluded due to antibody status

Source eCTD module 5.3.1.2, Study BDR12546, Table 18, page 69.

Table 52: Treatment ratio estimates (B/A and C/A) with 90% CI for total lixisenatide

Parameter	Comparison	Estimate	90% CI
C_{max}	B versus A	1.07	(0.95 to 1.21)
	C versus A	1.04	(0.93 to 1.15)
AUC_{last}	B versus A	1.30	(1.15 to 1.47)
	C versus A	1.45	(1.33 to 1.58)
AUC	B versus A	1.29	(1.15 to 1.46)
	C versus A	1.51	(1.36 to 1.67)

A = Lixisenatide 20 µg sc 200 µL, B = Lixisenatide 20 µg sc 100 µL, C = Lixisenatide 20 µg sc 50 µL

Note 1: AUC of subject 826001009 in period 3 (Treatment C) was excluded from analysis because AUC extrapolated was greater than 20%

Note 2: Period 2 of subject 826001005 (Treatment C) was excluded from analysis because treatment was given subdermally

Source eCTD module 5.3.1.2, Study BDR12546, Table 20, page 71.

There was no impact of information from this study on the proposed product label. In addition, the Sponsor mentioned in the Quality Overall Summary that the (b) (4) mg/mL dosage strengths were transferred (b) (4) and the manufactured batches of the 0.05 and 0.1 mg/mL dosage strengths were used in clinical trials.

(b) (4)

2.8.2 Dose-response relationship of different doses of lixisenatide on glucose profiles and gastric emptying (Study PDY12545)

The dose-response relationship of different doses of lixisenatide on postprandial plasma glucose following standardized liquid meal challenge compared to placebo was evaluated in study PDY12545. This study also evaluated the dose-response relationship of different doses of lixisenatide on postprandial insulin concentration compared to placebo, and the effect of different doses of lixisenatide on C-peptide, glucagon profiles and gastric emptying.

There was dose dependent decrease in fasting plasma glucose (FPG) following lixisenatide compared to placebo prior to the administration of the standardized liquid meal. Following administration of the meal, a dose-dependent reduction in PPG was demonstrated from the 2.5 µg dose up to the 20 µg dose compared to placebo. However, the effect appears to plateau around the 10 µg dose, as there was no substantial difference between the 10 and 20 µg doses (Figure 46). Within a period of 3 hours after meal challenge, the marked inhibitory effect on gastric emptying diminished at all dose levels, indicating that the major driver for the reduction of PPG excursion was the glucose independent slowing of gastric emptying.

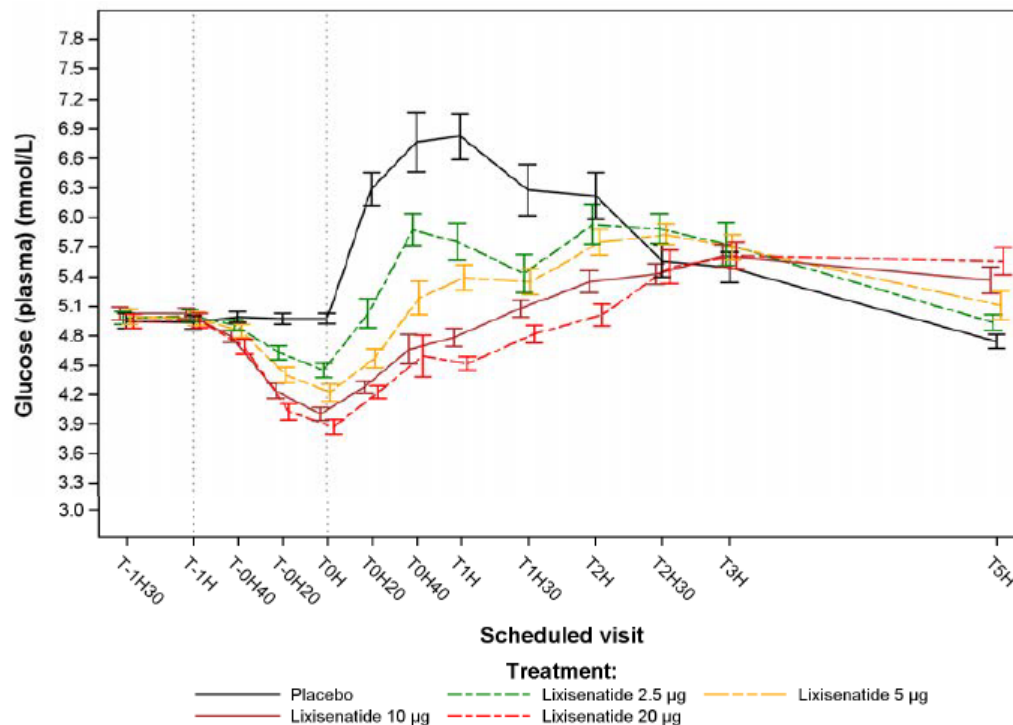


Figure 46: Plasma glucose (mmol/L) data from T-1H30 to T5H – Mean (+/- SEM)

Source eCTD module 5.3.4.1, Study PDY12545, Figure 3, page 56.

The mean differences between the 4 lixisenatide dose levels and placebo and the corresponding 90% CIs for the primary and secondary endpoints are provided in Table 53.

Table 53 Dose effect: Point estimates with 90% confidence intervals

Parameter	Group	Estimate	90% CI	p-value
Glucose (plasma) AUC ₀₋₁ (MMOL.MIN/L)	Lixisenatide 2.5 ug vs Placebo	-61.24	(-75.15 to -47.33)	<.001
	Lixisenatide 5 ug vs Placebo	-92.29	(-106.21 to -78.37)	<.001
	Lixisenatide 10 ug vs Placebo	-118.40	(-132.35 to -104.44)	<.001
	Lixisenatide 20 ug vs Placebo	-121.14	(-135.21 to -107.07)	<.001
	Lixisenatide 5 ug vs 2.5 ug	-31.05	(-44.74 to -17.35)	<.001
	Lixisenatide 10 ug vs 2.5 ug	-57.16	(-70.87 to -43.44)	<.001
	Lixisenatide 20 ug vs 2.5 ug	-59.90	(-73.82 to -45.99)	<.001
	Lixisenatide 10 ug vs 5 ug	-26.11	(-39.81 to -12.41)	0.002
	Lixisenatide 20 ug vs 5 ug	-28.86	(-42.78 to -14.93)	<.001
	Lixisenatide 20 ug vs 10 ug	-2.75	(-16.71 to 11.22)	0.744
Glucose (plasma) C _{max} (MMOL/L)	Lixisenatide 2.5 ug vs Placebo	-0.77	(-1.09 to -0.45)	<.001
	Lixisenatide 5 ug vs Placebo	-1.02	(-1.34 to -0.70)	<.001
	Lixisenatide 10 ug vs Placebo	-1.49	(-1.81 to -1.17)	<.001
	Lixisenatide 20 ug vs Placebo	-1.24	(-1.57 to -0.92)	<.001
	Lixisenatide 5 ug vs 2.5 ug	-0.25	(-0.56 to 0.07)	0.191
	Lixisenatide 10 ug vs 2.5 ug	-0.72	(-1.03 to -0.40)	<.001
	Lixisenatide 20 ug vs 2.5 ug	-0.48	(-0.79 to -0.16)	0.015
	Lixisenatide 10 ug vs 5 ug	-0.47	(-0.78 to -0.16)	0.015
	Lixisenatide 20 ug vs 5 ug	-0.23	(-0.55 to 0.09)	0.240
	Lixisenatide 20 ug vs 10 ug	0.24	(-0.08 to 0.56)	0.208
Insulin AUC ₀₋₁ (PMOL.MIN/L)	Lixisenatide 2.5 ug vs Placebo	-8648.18	(-12712.6 to -4583.72)	<.001
	Lixisenatide 5 ug vs Placebo	-16762.1	(-20848.1 to -12676.2)	<.001
	Lixisenatide 10 ug vs Placebo	-21895.9	(-25935.6 to -17856.2)	<.001
	Lixisenatide 20 ug vs Placebo	-24848.0	(-29078.3 to -20617.6)	<.001
	Lixisenatide 5 ug vs 2.5 ug	-8113.97	(-12173.1 to -4054.89)	0.001
	Lixisenatide 10 ug vs 2.5 ug	-13247.7	(-17214.2 to -9281.26)	<.001
	Lixisenatide 20 ug vs 2.5 ug	-16199.8	(-20262.3 to -12137.2)	<.001
	Lixisenatide 10 ug vs 5 ug	-5133.74	(-9169.99 to -1097.50)	0.038
	Lixisenatide 20 ug vs 5 ug	-8085.81	(-12321.6 to -3849.97)	0.002
	Lixisenatide 20 ug vs 10 ug	-2952.06	(-7049.25 to 1145.13)	0.234
Insulin C _{max} (PMOL/L)	Lixisenatide 2.5 ug vs Placebo	-100.52	(-215.68 to 14.63)	0.150
	Lixisenatide 5 ug vs Placebo	-277.18	(-390.80 to -163.57)	<.001
	Lixisenatide 10 ug vs Placebo	-428.34	(-542.53 to -314.16)	<.001
	Lixisenatide 20 ug vs Placebo	-388.44	(-508.72 to -268.17)	<.001
	Lixisenatide 5 ug vs 2.5 ug	-176.66	(-288.93 to -64.40)	0.011
	Lixisenatide 10 ug vs 2.5 ug	-327.82	(-439.52 to -216.12)	<.001
	Lixisenatide 20 ug vs 2.5 ug	-287.92	(-402.54 to -173.30)	<.001
	Lixisenatide 10 ug vs 5 ug	-151.16	(-262.85 to -39.47)	0.027
	Lixisenatide 20 ug vs 5 ug	-111.26	(-228.50 to 5.98)	0.118
	Lixisenatide 20 ug vs 10 ug	39.90	(-75.87 to 155.67)	0.567

For pharmacodynamic assessments, T0 reference is the meal challenge timepoint (i.e. 1 hour after lixisenatide administration).
Source eCTD module 5.3.4.1, Study PDY12545, Table 13, pages63-64.

An evaluation of post-prandial glucose showed that there was a dose-dependent reduction in PPG-C_{max} across the 2.5 µg to 10 µg lixisenatide doses compared to placebo. However, though mean PPG-C_{max} was higher for the 20 µg dose than the 10 µg dose, it was lower than the mean PPG-C_{max} for the 2.5 and 5 µg doses.

One hour after dosing of lixisenatide, a liquid meal was administered together with 1000 mg acetaminophen. The appearance of acetaminophen in plasma was reduced and delayed compared to placebo depending on the dose of lixisenatide administered, as acetaminophen was used as a probe for gastric emptying, which was delayed by lixisenatide in a dose-dependent manner.

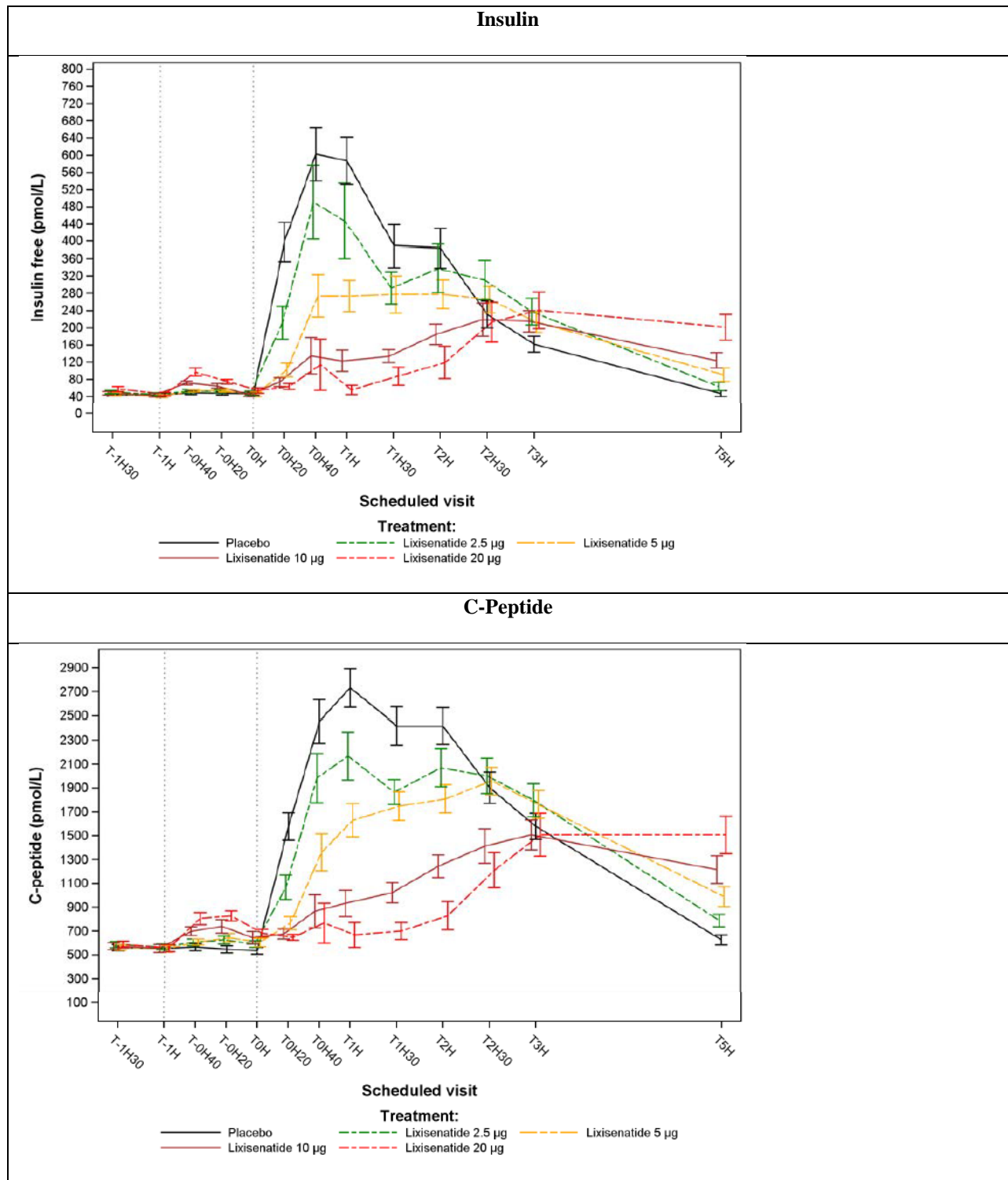


Figure 47: Mean ($\pm$ SEM) Insulin (pmol/L) and C-peptide (pmol/L) data from T-1H30 to T5H

Source eCTD module 5.3.4.1, Study PDY12545, Figure 10, page 73 and Figure 1, page 84.

As a consequence of the reduction in FPG, small and transient increases in insulin concentration were observed prior to the meal challenge following lixisenatide injection. Following the standardized liquid meal and corresponding to the reduction of PPG excursion, insulin secretion was reduced in a dose-

dependent manner up to 3 hours post meal challenge, supporting the delay in gastric emptying as the mode of action in this study ([Figure 47](#)). The 20 µg lixisenatide dose appeared to produce a more sustained delay in insulin secretion than the 10 µg dose.

Similar observations were also seen for C-peptide ([Figure 47](#)).

The exposure to lixisenatide increased with the dose injected, but over the dose range of 2.5 µg to 20 µg, exposure increased in a slightly less than dose-proportional manner.

The exposure-effect relationships (PK/PD) for the different PD parameters, showed that, in general, a plateau value representing the maximum effect in this study was reached with lixisenatide 20 µg, that did not differ greatly from that achieved with lixisenatide 10 µg. The results achieved with lixisenatide 5 µg tended to overlap with the 2 higher doses. The effect of the lixisenatide 2.5 µg dose produced only a marginal effect compared to placebo.

The influence of lixisenatide on the appearance of acetaminophen in plasma as a probe to show the extent of a delay of gastric emptying showed that the effect of the lixisenatide 10 µg dose did not completely reach the plateau, and the effect of the lixisenatide 2.5 µg dose over the 3 hours following dosing with acetaminophen was similar to that for placebo.

The results of the study reasonably support sponsor's interpretation of the data. However, the gastric emptying effects of lixisenatide have been reviewed in the initial submission of the NDA, and the findings of this study do not change our recommendation regarding co-administration of lixisenatide with other drugs.

2.8.3 Effect of lixisenatide on postprandial plasma glucose in pediatric (10 - 17 years old) and adult patients with type 2 diabetes (Study PKD11475)

The effects of a single subcutaneous lixisenatide dose of 5 µg and 10 µg as compared to placebo in reducing postprandial plasma glucose (PPG) assessed as area under the plasma glucose concentration curve after a standardized liquid meal (breakfast) in type 2 diabetic pediatric population (10-17 years old) and adults as controls was evaluated in study PKD11475.

The population to be studied comprised patients with T2DM, with or without a stable background metformin therapy, on a regimen of diet and exercise with an age ranging from 10 years to less than 18 years for the pediatric population and 18 to 65 years for the adult population.

In the pediatric evaluable PD population, the corrected plasma glucose-AUC_{0:30h-4:30h} was decreased by single doses of lixisenatide 5 and 10 µg compared to placebo, but the differences versus placebo were not statistically significant (Table 54). In addition, there was no statistically significant difference between lixisenatide 10 and 5 µg.

Table 54: Pediatric patients: summary of statistical analysis - plasma glucose corrected from premeal value AUC_{0:30h-4:30h} (mmol.h/L) - evaluable PD population

Parameter (unit)	Placebo (N=9)	Lixisenatide	
		5 µg (N=9)	10 µg (N=9)
Glucose (plasma) corrected pre-meal AUC _{0:30h-4:30h} (mmol.h/L)			
Number	9	9	9
Mean	10.10	6.24	8.76
SD	9.57	8.53	8.12
SEM	3.190	2.844	2.705
Median	7.89	3.77	4.63
Min : Max	-2.1 : 21.7	-3.2 : 19.9	-0.3 : 24.1
LS Mean (SE)	9.63 (3.95)	5.72 (3.99)	8.11 (4.08)
95% CI	(-0.80 to 20.06)	(-4.67 to 16.10)	(-2.29 to 18.52)
LS Mean difference (SE) vs. Placebo ^a		-3.92 (1.97)	-1.52 (1.89)
95% CI		(-8.17 to 0.34)	(-5.59 to 2.56)
p-value		0.0681	0.4359
LS Mean difference (SE) vs. lixisenatide 5 µg			2.40 (2.30)
95% CI			(-2.57 to 7.37)
p-value			0.3162

CI = Confidence interval, SE = Standard error

^aDifference: Lixisenatide 5 µg - Placebo and Lixisenatide 10 µg - Placebo respectively

Note: The linear fixed effects model used includes treatment, sequence and period as fixed effects, and patient-within-sequence as random effect, and the corresponding pre-meal value (T0.5h) as covariate.

Number corresponds to the count of patients with available data

Source eCTD module 5.3.4.2, Study PDY11475, Table 21, page 72.

The change from pre-meal plasma glucose concentration following lixisenatide 5 µg and 10 µg doses compared to placebo in pediatric patients is shown in Figure 48.

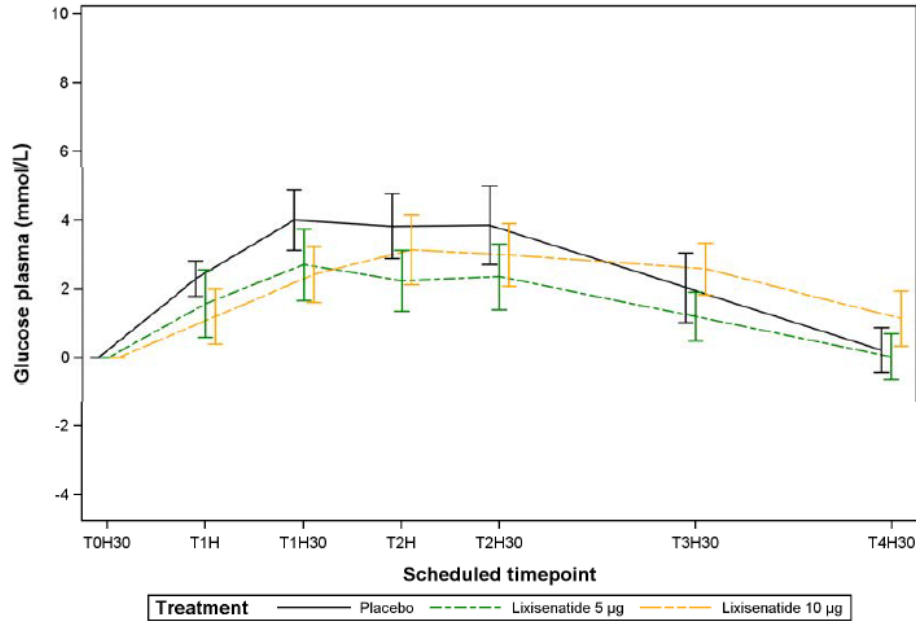


Figure 48: Mean ($\pm$ SE) plasma glucose concentration in pediatric patients: change from premeal - evaluable PD population

Source eCTD module 5.3.4.2, Study PDY11475, Figure 2, page 73.

In the adult evaluable PD population, a dose-dependent reduction in corrected plasma glucose-AUC_{0:30h-4:30h} was observed with single doses of lixisenatide 5 and 10 µg compared to placebo. The LS mean difference between lixisenatide 10 and 5 µg was not statistically significant ([Table 55](#)).

Table 55: Summary of statistical analysis in Adult patients - plasma glucose corrected from premeal value AUC_{0:30h-4:30h}- evaluable PD population

Parameter (unit)	Placebo (N=12)	Lixisenatide	
		5 µg (N=12)	10 µg (N=12)
Glucose (plasma) corrected pre-meal AUC _{0:30-4:30h} (mmol.h/L)			
Number	12	12	12
Mean	17.51	10.60	1.89
SD	4.98	6.83	8.36
SEM	1.437	1.971	2.412
Median	16.50	12.08	1.01
Min : Max	9.7 : 25.7	-5.1 : 18.6	-15.9 : 16.3
LS Mean (SE)	16.60 (2.46)	8.03 (2.95)	1.11 (2.85)
95% CI	(11.21 to 21.98)	(1.79 to 14.26)	(-4.91 to 7.14)
LS Mean difference (SE) vs. Placebo ^a		-8.57 (3.05)	-15.48 (2.93)
95% CI		(-14.91 to -2.23)	(-21.59 to -9.38)
p-value		0.0104	<.0001
LS Mean difference (SE) vs. lixisenatide 5 µg			-6.91 (3.68)
95% CI			(-14.59 to 0.77)
p-value			0.0752

CI = Confidence interval, SE = Standard error

^aDifference: Lixisenatide 5 µg - Placebo and Lixisenatide 10 µg - Placebo respectively

Note: The linear fixed effects model used includes treatment, sequence and period as fixed effects, and patient-within-sequence as random effect, and the corresponding pre-meal value (T0.5h) as covariate.

Number corresponds to the count of patients with available data
Source eCTD module 5.3.4.2, Study PDY11475, Table 23, pages 76-77.

The change from pre-meal plasma glucose concentration following lixisenatide 5 µg and 10 µg doses compared to placebo in adult patients is shown in [Figure 49](#).

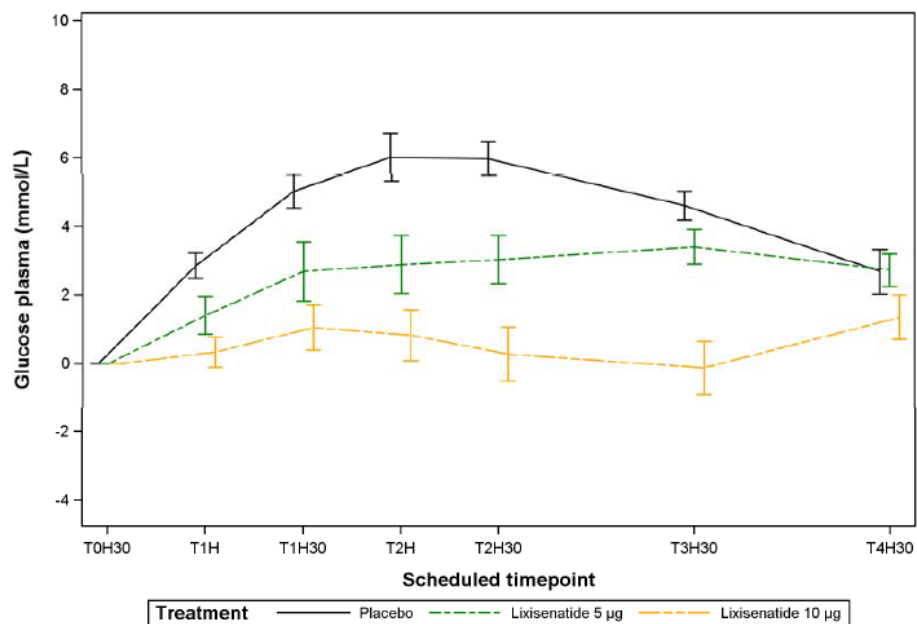


Figure 49: Change from premeal mean ($\pm$ SE) plasma glucose concentration in adult patients-evaluable PD population

Source eCTD module 5.3.4.2, Study PDY11475, Table 23, pages 76-77.

Following single subcutaneous administration, lixisenatide exposure was similar for both dose groups in the evaluable pediatric patients, whereas in adult patients, the lixisenatide exposure increased dose-proportionally. In the pediatric PK population, lixisenatide exposure was slightly higher for the higher dose of 10 µg. In pediatric patients, the exposure was similar to that in adults for lixisenatide 5 µg, but lower for lixisenatide 10 µg.

2.8.4 Effect of repeated doses of lixisenatide 20 µg QD on postprandial plasma glucose compared to liraglutide 1.2 mg QD or 1.8 mg QD (Study PDY12625)

The effects of repeated subcutaneous doses of lixisenatide 20 µg once daily (QD) as compared to liraglutide 1.2 mg QD or 1.8 mg QD in reducing postprandial plasma glucose assessed as area under the plasma glucose-concentration-time curve after a standardized breakfast at the end of an 8-week treatment period in patients with type 2 diabetes mellitus (T2DM) not adequately controlled with insulin glargine (with or without metformin) was investigated in study PDY12625.

Male and female patients, 18 to 75 years, inclusive, with T2DM, diagnosed at least 1 year at the time of the screening visit, not adequately controlled with insulin glargine alone or combined with or NPH alone or combined with a stable dose of metformin with or without a dipeptidyl peptidase-4 (DPP-4) inhibitor or a sulfonylurea were enrolled in this study.

The mean 24-hour plasma glucose profiles, based on 17-time point assessments, were similar across the 3 treatment groups at baseline (Day -3). On Day 56 (Week 8), greatest reductions with lixisenatide were seen postbreakfast (only up to 4 hours and 30 minutes after injection of lixisenatide); after this period, plasma glucose levels were similar to baseline values (Figure 50). Treatment with liraglutide (1.2 and 1.8 mg), however, resulted in consistent glucose reductions throughout the day.

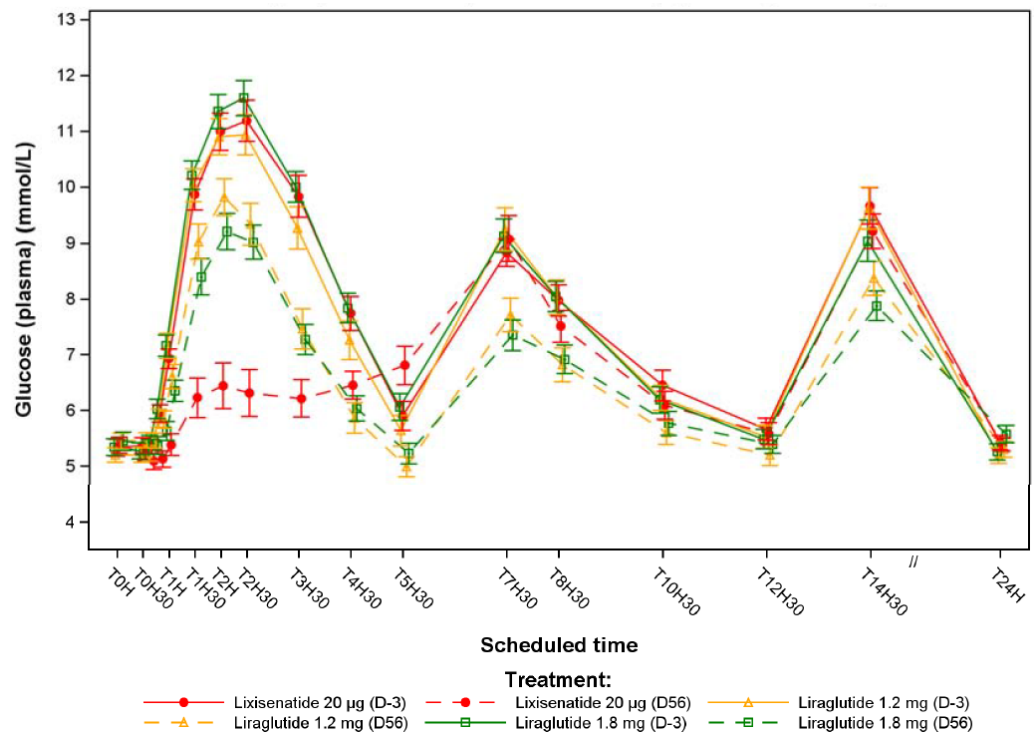


Figure 50: Mean (± SE) concentrations for 24-hour plasma glucose profiles (mmol/L) on Day -3 and Day 56 - PD population

Source eCTD module 5.3.4.2, Study PDY12625, Figure 5, page 105.

The primary endpoint of this study was a comparison of the performance of lixisenatide against liraglutide in reducing PPG AUC between 0:30 and 4:30 h after a standardized solid breakfast. Lixisenatide demonstrated a greater effect than liraglutide (1.2 and 1.8 mg) in reducing PPG AUC_{0:30–4:30h} after a standardized solid breakfast, however, liraglutide exhibited a sustained plasma glucose decrease at

lunch and dinner times. The greater decrease in plasma glucose after breakfast in lixisenatide-treated patients can probably be related to the significant delayed gastric emptying following lixisenatide compared to liraglutide.

The profiles of corrected C-peptide concentrations from the start of standardized solid breakfast (T0H30 post lixisenatide injection) up to 5 hours later (T5H30 post injection) were similar on Day -3 (baseline) in all treatment groups with a peak increase in C-peptide concentrations 2 hours after breakfast (T2H30) ([Figure 51](#)). On Day 56, the corrected C-peptide concentrations were lower compared to Day -3 values up to 3 hours postbreakfast (T3H30 post lixisenatide injection) but were slightly higher at 5 hours postbreakfast (T5H30 post lixisenatide injection). In both liraglutide 1.2 and 1.8 mg groups, corrected C-peptide concentrations were higher compared to Day-3 (baseline) up to 5 hours post-breakfast (T5H30) with a peak at 2 hours postbreakfast (T2H30 post IMP injection) in the liraglutide 1.2 mg group and at 3 hours postbreakfast (T3H30 post IMP injection) in the liraglutide 1.8 mg group.

On Day -3, peak in corrected glucagon concentrations were observed approximately 30 minutes post-breakfast in all treatment groups ([Figure 51](#)). On Day 56, corrected glucagon concentrations were lower compared to baseline (Day -3) in all treatment groups during the first hour after breakfast ingestion (up to T1H30 post injection), with peak values observed at approximately 10 minutes postbreakfast (T0H40 post injection) in the lixisenatide group and at approximately 30 minutes post-breakfast (T1H post injection) in the liraglutide 1.2 and 1.8 mg groups.

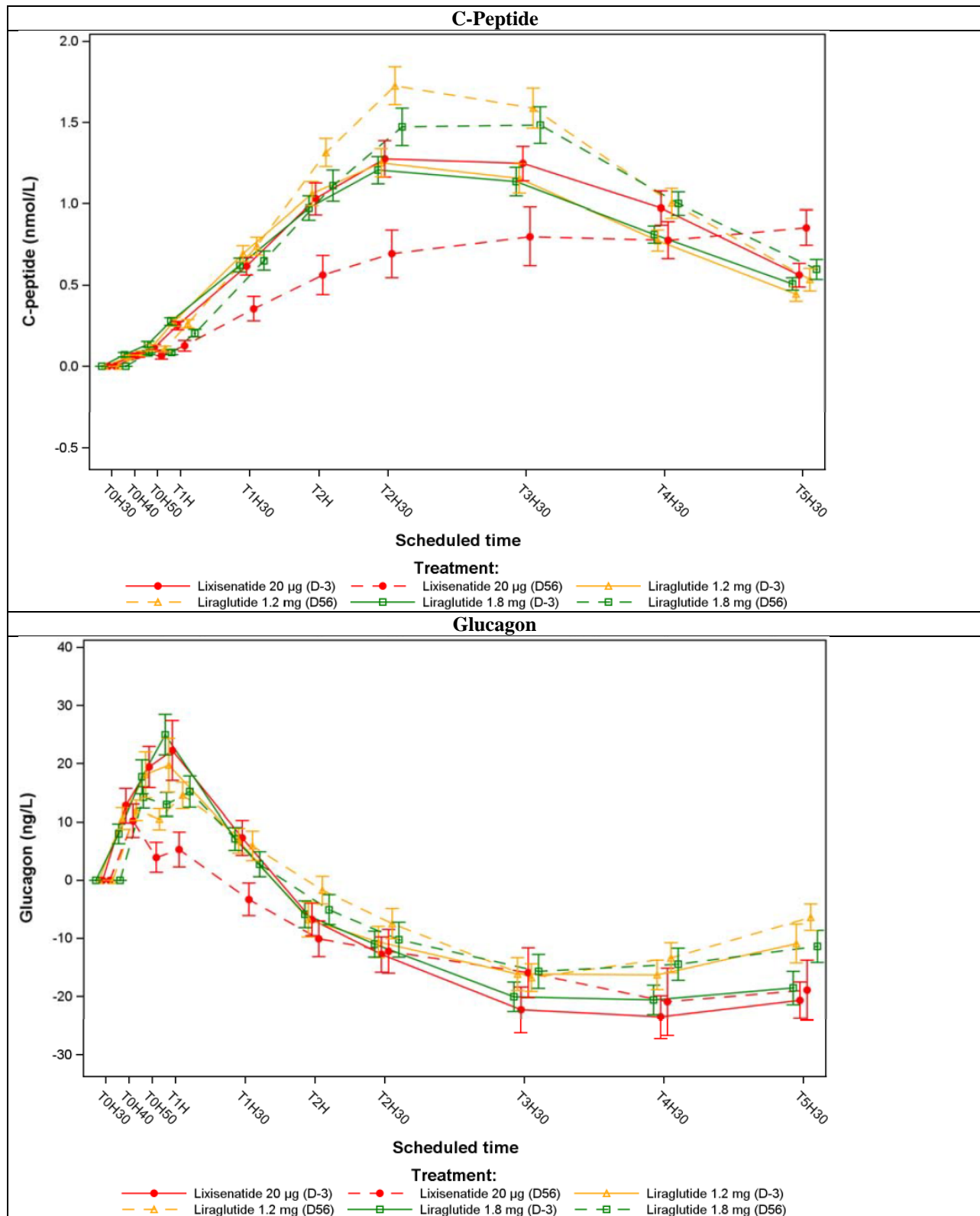


Figure 51: Mean ($\pm$ SE) concentrations for corrected C-peptide and Glucagon on Day -3 and Day 56 – PD population

Source eCTD module 5.3.4.2, Study PDY12625, Figure 9, page 115 and Figure 11, Page 120.

After 8 weeks of treatment, both HbA_{1c} and body weight were decreased in the 3 treatment groups. Reductions from baseline in HbA_{1c} and body weight were comparable for lixisenatide 20 µg and liraglutide 1.2 mg, while liraglutide 1.8 mg demonstrated greater reductions in HbA_{1c} and body weight compared to lixisenatide.

The results of this study provide useful insight into the mechanism of action of lixisenatide. However, the results for the initial 4.5 hour post-prandial glucose reduction were consistent with the observations from the single dose PK/PD study PDY12545. Sponsor used the data from this study to support the labeling claims for PPG reduction. However, in comparison to liraglutide, the effect of lixisenatide on PPG reduction seems limited to initial 4 hours and data does not demonstrate sustained reduction as observed for the liraglutide doses. The utility of the post-breakfast PPG reduction in the overall efficacy of lixisenatide is not fully understood.

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4 APPENDIX

4.1 Pharmacometric Review

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OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 Summary of Findings

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does the dose-response relationship for efficacy and safety support the proposed dose and dosing regimen of 20 µg once daily?

Yes, the dose-response relationship of efficacy and safety supports the proposed dosing regimen of 20 µg once daily because of the following reasons:

Efficacy:

- In the dose ranging Phase 2 study, a clear dose response relationship was observed, where increasing doses from 5 µg to 30 µg, within the QD and BID-dosing regimen resulted in increase in response in terms of HbA_{1c} (Figure 1).
- Compared to proposed 20 µg QD dosing, 10 µg BID-dosing regimen showed numerically slightly higher reduction in HbA_{1c}. However, the added benefit with 10 µg BID-dosing should be weighed against narrow time window left for the administration of concomitant medication because of the effect of lixisenatide on delaying gastric emptying time. Furthermore, as seen in Figure 2 cumulative distribution plots for change from baseline HbA_{1c} is highly overlapped between the these two dosing regimens.
- Compared to 10 µg BID dose, 20 µg QD dose showed a numerically greater change in weight loss.

Safety

- In the dose ranging Phase 2 study, doses higher than 20 µg in both QD and BID dosing regimen resulted in more gastrointestinal related adverse events (Table 1).
- Additionally, compared to 20 µg QD dosing regimen 10 µg BID dosing regimen had less gastrointestinal related side effects. However, as stated above the added safety benefit with BID dosing regimen needs to be counterbalanced with the inconvenience of co-administration of other drugs.

Practicality

- Lixisenatide delays the gastric emptying time and hence concomitant medications need to be administered (b) (4) 1 hr before lixisenatide administration or with next meal for those drugs that have to be administered with food.
- Thus, with BID dosing regimen the subjects will have very little window for taking concomitant medication and hence we agree with the sponsor's proposed 20 µg QD dosing regimen as acceptable from a practical standpoint.

Furthermore, in all the Phase 3 trials sponsor had only studied 20 µg QD dosing making it difficult to compare QD and BID doses beyond this 13 week Phase 2 trial.

Summarized below are the dose-response relationships of efficacy and safety in detail.

Dose-Response Analysis for Efficacy

The sponsor studied only one dose of 20 µg QD in all the Phase 3 trials. Also, the trough concentrations data in the Phase 3 trials were below the limit of quantification. Thus, dose/exposure response relationship for safety and efficacy is limited to data available from a single Phase 2 trial of 13-week duration (Study #DRI6012).

The selection of 20 µg QD dose in all the Phase 3 trials, was primarily based on a Phase 2 dose ranging study of 13-week treatment duration (Study #DRI6012). In this Phase 2 study, subjects were randomized to receive 5 µg, 10 µg, 20 µg, and 30 µg of lixisenatide dose as QD and BID dosing regimen. The primary efficacy endpoint for this Phase 2 study was change from baseline in HbA_{1c} at week 13. As shown in Figure 1, a clear dose-response relationship was observed, where increasing doses within the QD and BID-dosing regimen resulted in increase in response in terms of HbA_{1c}. Compared to proposed 20 µg QD dosing, 10 µg BID-dosing regimen showed slight numerically greater reduction in HbA_{1c} (-0.69 with 20 µg QD vs. -0.78 with 10 µg BID-dosing). Furthermore, Figure 2 shows cumulative distribution function (CDF) plots for change from baseline HbA_{1c} between these two dosing regimens. Overlapping CDF plots between 20 µg QD and 10 µg BID dosing indicates that the distribution for change from base line in HbA_{1c} is similar across both the dosing group (Figure 2).

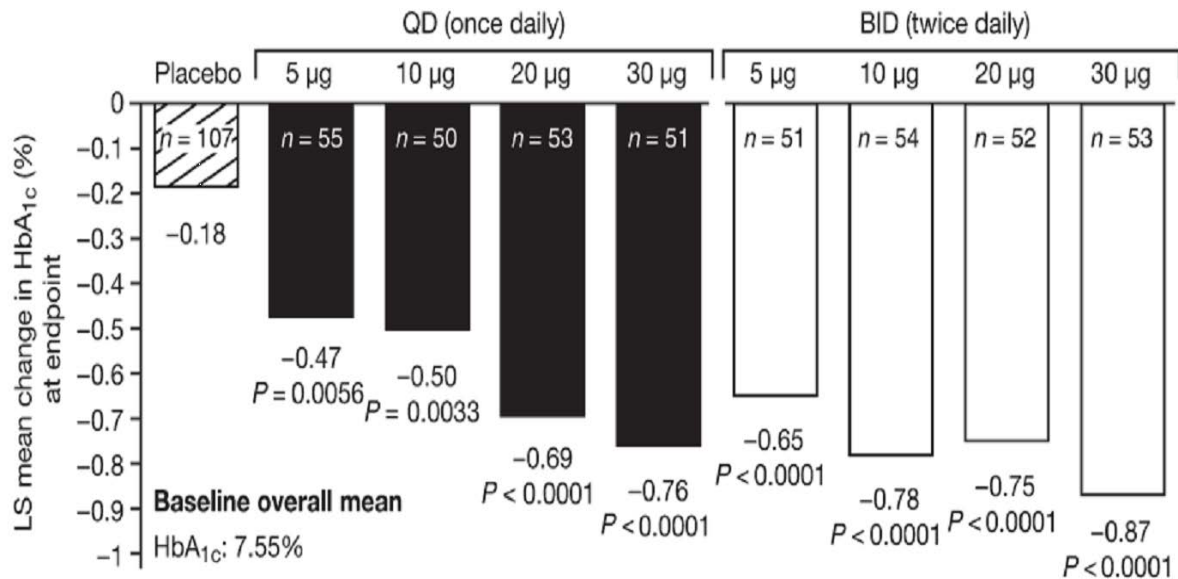


Figure 1: Mean change in HbA_{1c} at endpoint (ITT population) (Study DRI6012)

BID = twice daily; HbA_{1c} = glycosylated hemoglobin; ITT = intent-to-treat; LS = least square; n = number of patients; QD = once daily

Source: Sponsor's Summary of Clinical Efficacy report Pg 131

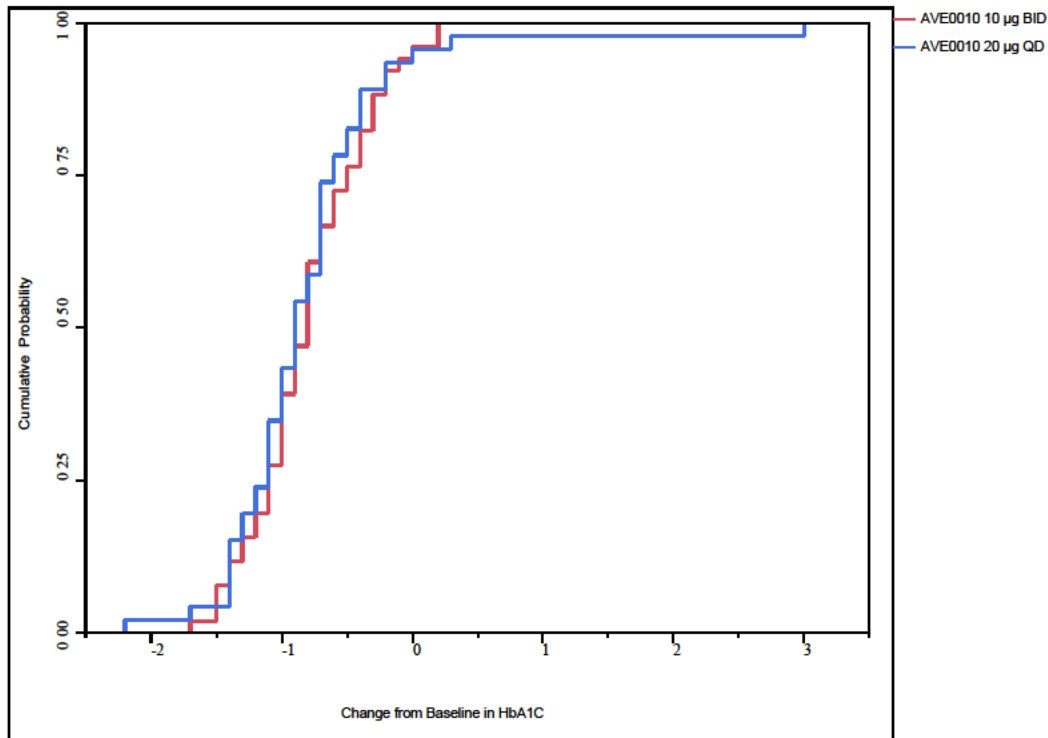
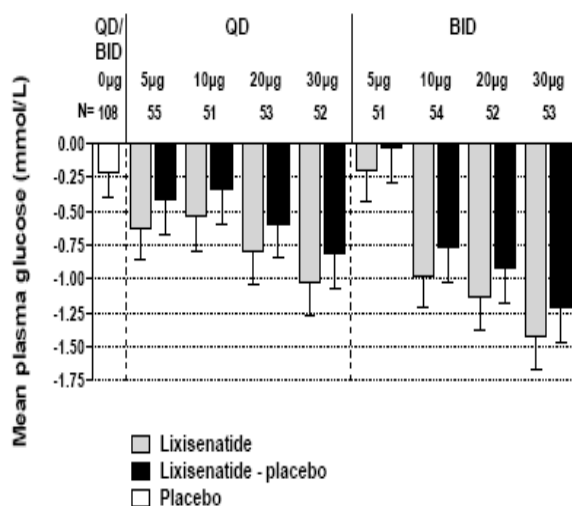


Figure 2: Cumulative distribution function plot for mean change from baseline in HbA1c at week 13 (Study DRI6012).

AVE0010 10 µg BID = Lixisenatide 10 µg BID dosing; AVE0010 20 µg QD = Lixisenatide 20 µg QD dosing

Figure 3, represents the dose-response relationship for secondary pharmacodynamic endpoints: A) fasting plasma glucose (FPG) and B) 2-hr post prandial glucose (PPG) at week 13. A clear dose response relationship was observed for both secondary endpoints, where increasing doses within the QD and BID-dosing regimen resulted in increase in response. Compared to proposed 20 µg QD dosing, 10 µg BID-dosing regimen showed numerically greater reduction in FPG whereas for PPG 20 µg QD dosing seemed to be numerically better than 10 µg BID dosing. Lixisenatide has a short plasma half life of around 2-4 hours. Thus, better control of FPG is expected with BID dosing of lixisenatide since BID dosing can provide glucose control at both morning and evening meal resulting in better FPG with BID dosing. In addition, better effect on PPG with 20 µg QD dose is expected since with QD dosing 20 µg of dose is given at once before meal and hence more effect on PPG as compared to BID dosing where the 20 µg dose is divided into morning and evening dose of 10 µg each.

A



B

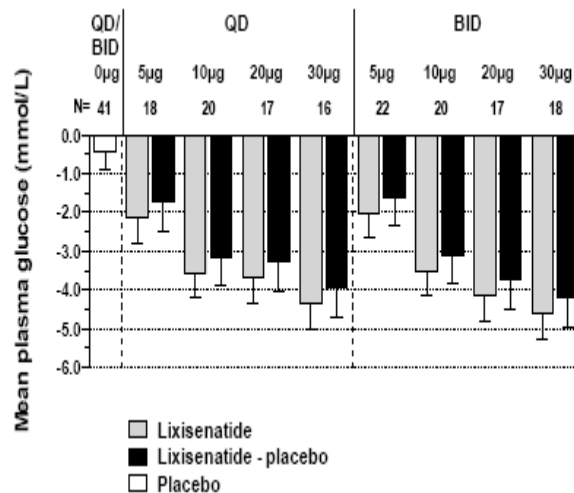


Figure 3: Mean change from baseline in A) fasting plasma glucose B) 2 hour post prandial glucose (Study DRI6012)

BID = twice daily; n = number of patients; QD = once daily

Source: Sponsor's Summary of Clinical Pharmacology report Pg 118

Dose-Response relationship for Weight Loss: A clear dose-response relationship for weight loss was observed for each dosing regimen, i.e., the higher the lixisenatide dose within a regimen (QD or BID) the larger the mean decrease in body weight. Figure 4 shows the mean ($\pm$ SE) change in body weight by time and by treatment group. The data for mean change in weight (kg) from baseline to endpoint (week 13) is presented in Table 1. Compared to 10 µg BID dose, 20 µg QD dose has a greater weight loss change.

Table 1: Mean change in weight (kg) from baseline to endpoint – ITT population in Phase 2 Trial (Study#DRI6012)

	QD Dosing					BID Dosing			
	Placebo (n=108)	5 µg (n=55)	10 µg (n=51)	20 µg (n=53)	30 µg (n=52)	5 µg (n=51)	10 µg (n=54)	20 µg (n=52)	30 µg (n=53)
Baseline Mean (SD) Weight (kg)	87.66 (13.69)	84.83 (15.56)	90.66 (17.37)	88.93 (17.11)	87.17 (15.19)	86.26 (14.41)	90.02 (16.90)	88.18 (16.76)	87.55 (13.74)
Change from Baseline Mean (SD) Weight (kg)	-1.51 (2.22)	-1.51 (2.65)	-2.02 (2.64)	-2.59 (3.14)	-3.02 (2.86)	-1.65 (2.56)	-1.85 (2.74)	-2.18 (2.15)	-3.43 (2.68)

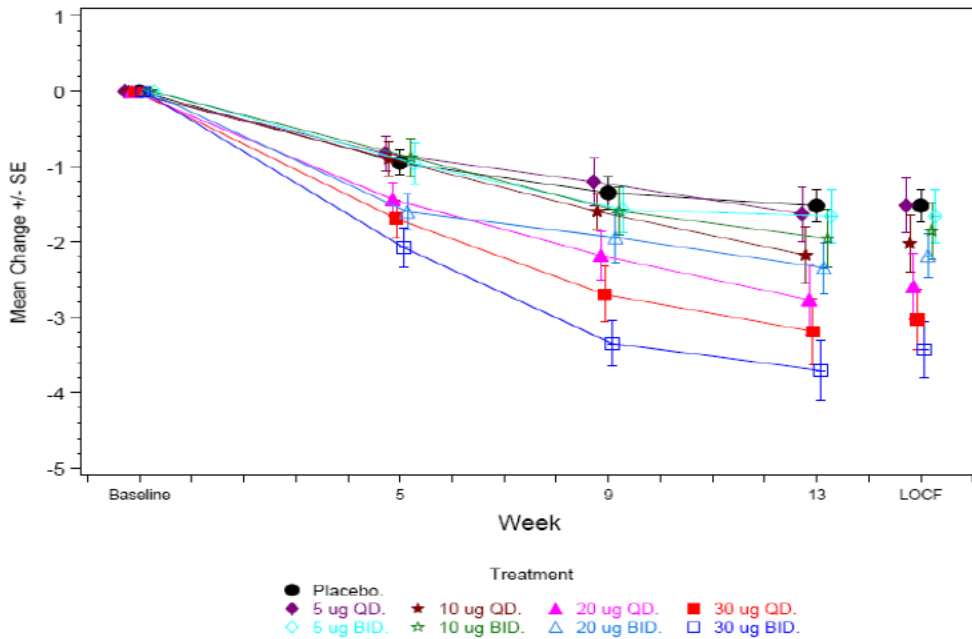


Figure 4: Mean ($\pm$ SE) Change in Weight (kg) by Visit and at Endpoint – ITT Population

BID = twice daily; QD = once daily

Source: Sponsor's Study report for DRI6012 Pg 88

Dose Response relationship for safety

- **Gastrointestinal Disorder:** A clear dose-response relationship within both regimens was seen in the number of subjects with GI related adverse events. The frequencies for GI side effects ranged from 21.8 % (5 μ g) to 51.9 % (30 μ g) in lixisenatide QD groups and from 22.6% (5 μ g) to 57.4 % (30 μ g) in lixisenatide BID groups. Doses higher than 20 μ g in both QD and BID dosing regimen resulted in more gastrointestinal related adverse events (Table 2). Additionally, compared to 20 μ g QD dosing regimen 10 μ g BID dosing regimen has less gastrointestinal related side effects.

	QD Dosing					BID Dosing			
	Plb (109)	5 μ g (55)	10 μ g (52)	20 μ g (55)	30 μ g (54)	5 μ g (53)	10 μ g (56)	20 μ g (54)	30 μ g (54)
Subjects with any TEAEs (% of Subjects)	65 (29%)	31 (56.4%)	26 (50%)	37 (67.3%)	42 (77.8%)	30 (56.6%)	32 (57.1%)	38 (70.4%)	40 (74.1%)
Gastrointestinal Disorders (% of Subjects)	21 (19%)	12 (21.8%)	11 (21.2%)	23 (41.8%)	28 (51.9%)	12 (22.6%)	15 (26.8%)	25 (46.3%)	31 (57.4%)

- **Effect on Heart Rate:** Lixisenatide was not found to affect the heart rate. Heart rate results at baseline and end of treatment are shown in Table 3. There was no significant change in the heart rate from baseline to end of study in any treatment group. No difference in heart rate was observed between 20 µg QD dose and 10 µg BID dose. Also, in thorough QT study no difference in heart rate was observed following 20 µg QD dose and 30 µg BID dose. Please refer to QT-IRT review dated 06/06/12 under IND62724.

Table 3: Mean change in Heart Rate (bpm) from baseline to endpoint - Safety population

	QD Dosing				BID Dosing				
	Placebo (N=109)	5 µg (N=55)	10 µg (N=52)	20 µg (N=55)	30 µg (N=54)	5 µg (N=53)	10 µg (N=56)	20 µg (N=54)	30 µg (N=54)
Baseline									
N	109	54	51	54	54	52	55	53	54
Mean (SD)	74.34 (8.28)	73.02 (8.31)	73.04 (8.14)	73.37 (9.45)	75.39 (11.10)	75.40 (9.16)	73.16 (9.07)	77.02 (10.82)	73.39 (9.61)
Median	73.00	72.00	73.00	72.00	74.00	77.50	72.00	77.00	72.00
Min : Max	57.0 : 95.0	55.0 : 95.0	54.0 : 90.0	56.0 : 102.0	56.0 : 106.0	60.0 : 100.0	50.0 : 92.0	50.0 : 112.0	51.0 : 110.0
Endpoint									
N	109	54	51	54	54	52	55	53	54
Mean (SD)	74.80 (9.51)	74.15 (9.58)	72.61 (9.21)	72.94 (9.20)	75.26 (10.95)	74.79 (10.03)	73.13 (6.98)	78.06 (10.95)	74.56 (9.37)
Median	74.00	72.00	72.00	72.00	74.00	72.00	72.00	78.00	76.00
Min : Max	56.0 : 104.0	59.0 : 100.0	48.0 : 96.0	56.0 : 100.0	54.0 : 107.0	50.0 : 113.0	56.0 : 90.0	53.0 : 110.0	52.0 : 100.0
Change									
N	109	54	51	54	54	52	55	53	54
Mean (SD)	0.46 (9.56)	1.13 (8.33)	-0.43 (9.14)	-0.43 (9.35)	-0.13 (9.99)	-0.62 (11.02)	-0.04 (8.30)	1.04 (10.73)	1.17 (10.32)
Median	1.00	0.00	-2.00	0.00	-0.50	-1.00	0.00	1.00	1.50
Min : Max	-24.0 : 24.0	-18.0 : 24.0	-18.0 : 26.0	-28.0 : 20.0	-20.0 : 37.0	-20.0 : 45.0	-16.0 : 30.0	-28.0 : 30.0	-20.0 : 28.0

Source: Sponsor's Study report for DRI6012 Pg 148

In summary, a clear dose response was observed for efficacy and GI safety. Increasing doses within QD and BID dosing regimen resulted in increase in primary efficacy parameter, i.e. change from baseline in HbA1c. Secondary efficacy parameter such as fasting plasma glucose and post prandial glucose also showed dose response relationship. Similar trend of dose response was observed for GI related safety. Increasing dose in both QD and BID dosing regimen resulted in higher GI related incidences. Doses higher than 20 µg in both QD and BID dosing regimen resulted in more gastrointestinal related adverse events and thus not tested in Phase 3 program

1.1.2 Does the dose-response relationship for efficacy and safety supports the proposed 1-step dosing recommendation of starting dose of 10 µg QD for 14 days followed by maintenance dose of 20 µg QD?

Yes, sponsor's proposal for 1-step dosing recommendation of starting dose of 10 µg QD for 14 days followed by maintenance dose of 20 µg QD is acceptable from efficacy and safety standpoint. The following reasons support our recommendations:

1. Similar Efficacy: In two Phase 3 studies, 1-step and 2-step dose increases resulted in similar efficacy (Figure 5).
2. Similar GI Adverse Event Profile: Time to GI event for initial 30 days in two Phase 3 trials showed no difference in GI related adverse events in both the dosing regimen (Figure 6).

In majority of the Phase 3 trials, the sponsor used a 2-step dosing regimen. In the 2-step dosing the patients were started with the initiation dose of 10 µg QD lixisenatide for 1 week followed by 15 µg QD for 1 week, and subsequently 20 µg QD as a maintenance dose. Later in the development phase sponsor used a 1-step dosing regimen, which is also the current proposed dosing recommendation in the product label. In the 1-step dosing regimen, patients were given 10 µg dose for 2 weeks followed by 20 µg QD maintenance dose. To evaluate the impact of 1-step vs. 2-step dose increase on efficacy and safety, sponsor conducted two Phase 3 trials.

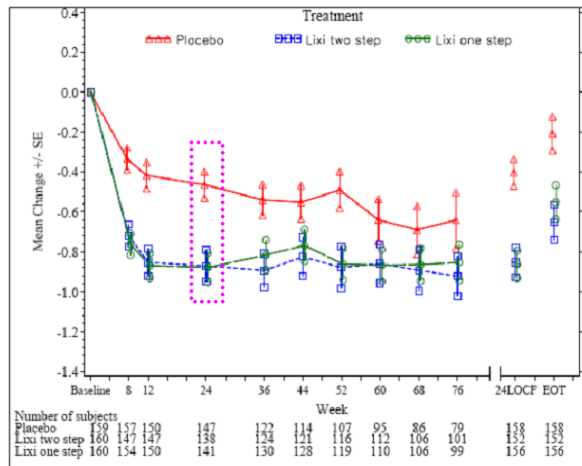
Effect of 1-Step vs 2-Step Dose Increase on Efficacy

Sponsor's analysis of the 1-step and 2-step dose initiation in two Phase 3 studies, EFC6018 and EFC10743 is shown in Figure 5. Sponsor showed that a significant HbA_{1c} reduction from baseline of similar magnitude with both dose increase regimens (-0.85% for the 1-step group and -0.73% for the 2-step group in Study EFC6018; -0.83% for the 2-step group and -0.92% for the 1-step group in Study EFC10743). Thus, based on sponsor's analysis, 1-step and 2-step dose initiation regimens were similar in terms of efficacy. Such similarity in results were expected since the only difference between the two groups was a higher dose (15 µg compared with 10 µg) during the second week of treatment.

Effect of 1-Step vs 2-Step Dose Increase on Safety

Survival plot for comparing time to GI event in two Phase 3 trials showed no difference in GI related adverse events in both the dosing regimen (Figure 6). We evaluated time to gastrointestinal adverse events in both 1-step and 2- step dosing regimen. The only difference in 1-step vs. 2-step dosing regimen is a higher dose 15 µg (compared with 10 µg in 1-step) during the second week of treatment. After the second week of treatment, both the dose groups had same maintenance dose of 20 µg QD. Survival plot for comparing time to GI event in two Phase 3 trials showed no significant differences in GI related adverse events in both the dosing regimen (Figure 6).

Study EFC10743



Study EFC6018

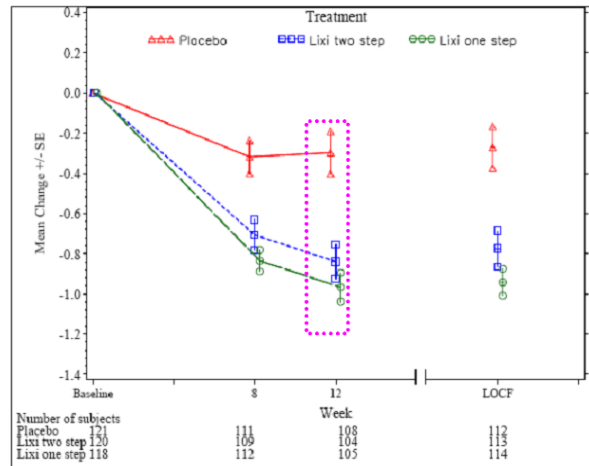
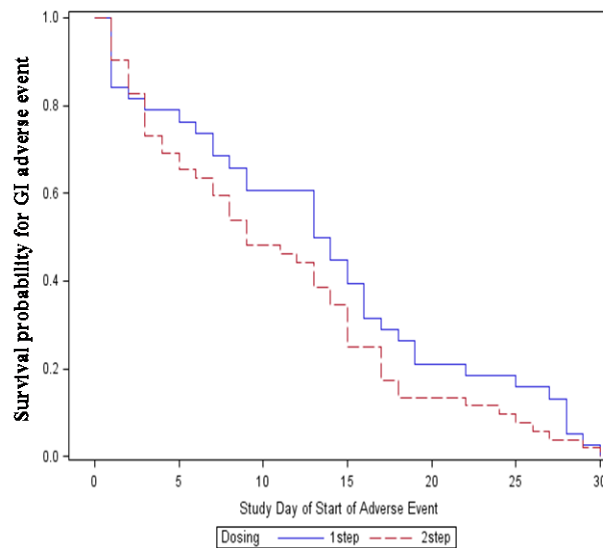


Figure 5: Time-profiles for adjusted mean change from baseline in HbA1c in Phase 3 trials EFC10743 (left) and EFC60182 (right) upon administration as placebo (red), lixisenatide 20 µg QD dose administered as one step (green), and 20 µg QD dose administered as two steps (blue)

Source: Sponsor's Summary of Clinical Efficacy report Pg 149

Phase 3 Trial (10743)

Time to First GI Event (30 Days)



Phase 3 Trial (6018)

Time to First GI Event (30 Days)

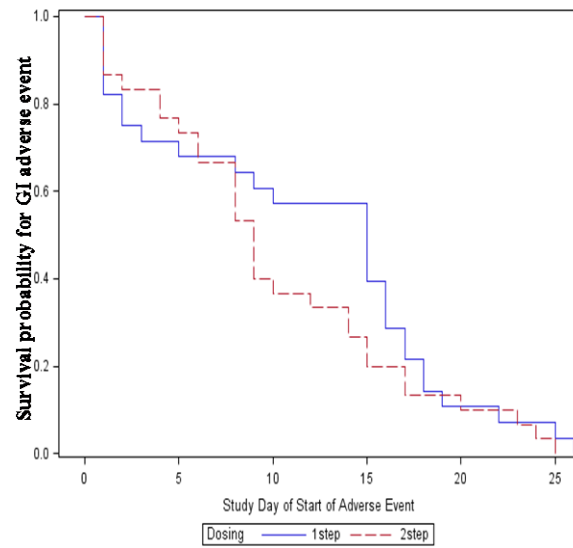


Figure 6: Survival plot for time to GI event in first 30 days of the treatment in Phase 3 trials EFC10743 (left) and EFC60182 (right). Lixisenatide 20 µg QD dose administered as one step (blue), and 20 µg QD dose administered as two steps (red).

1.1.3 What is the impact of Anti-drug antibody on efficacy?

- Is it possible to identify the patient population early on that are likely to be non-responders?

- Higher antibody concentrations resulted in attenuated HbA_{1c} response. Antibody concentration response analysis (Figure 7), showed a lower change from baseline in HbA_{1c} with increasing antibody concentrations based on week 4 and week 24 antibody concentrations.
- No correlation was observed between week 4 and week 24 antibody data (Figure 8). Since the week 4 antibody data is not predictive of week 24 antibody data, the analysis of antibody concentration to efficacy is exploratory in nature and cannot identify non responders early on with the drug treatment.

Antibody Effect on Efficacy

In Phase 1, Phase 2, and Phase 3 trials, sponsor observed formation of lixisenatide anti-drug antibody. To evaluate the potential neutralizing effect of anti-lixisenatide antibodies on efficacy, sponsor conducted a meta-analysis based on the pooled data from eight pivotal Phase 3 studies with at least 24-week treatment that collected the antibody data (Studies EFC6014, EFC6015, EFC6016, EFC6017, EFC10743, EFC10781, EFC10887 and EFC11321).

Meta analysis results showed (Table 4) that at the end of the main treatment period (Week 24), anti-lixisenatide antibody status along with concomitant HbA_{1c} value was available in 1954 patients from the lixisenatide group, including 1333 (68.2%) patients assessed as antibody-positive, and 621 (31.8%) assessed as antibody-negative. Overall the LS mean change in HbA_{1c} from baseline was similar regardless of the antibody status (-0.82% [95% CI: -0.895 to -0.755] in antibody-positive patients and -0.83% [95% CI: -0.920 to -0.746] in antibody-negative patients).

Overall, 1475 (78.0%) patients were either assessed as antibody negative or had an antibody concentration <LLOQ (3.21 nmol/L), and the LS mean change in HbA_{1c} from baseline was -0.86% (95% CI: -0.930 to -0.795) in these patients. The LS mean change in HbA_{1c} from baseline was -0.64% (95% CI: -0.751 to -0.528) in the group of patients with a quantifiable antibody concentration ≤100 nmol/L, and it was -0.16% (95% CI: -0.418 to 0.096) in the group of 45 (2.4%) patients with antibody concentration >100 nmol/L (Table 4).

Table 4: Meta analysis of change in HbA1c (%) from baseline to Week 24 by anti lixisenatide antibody status and concentration based on pooled data of 8 pivotal phase 3 placebo-controlled studies - mITT population.

Source: Sponsor's Summary of Clinical Efficacy report Pg 126 Table 19.

	Lixisenatide			
	n/N (%)	LS Mean ^b	SE ^b	95% C.I. ^b
Anti-lixisenatide antibody status ^a				
Positive	1333/1954 (68.2%)	-0.82	0.036	(-0.895 to -0.755)
Negative	621/1954 (31.8%)	-0.83	0.044	(-0.920 to -0.746)
Anti-lixisenatide antibody concentration ^c				
Antibody negative	621/1890 ^d (32.9%)			
<LLOQ	854/1890 ^d (45.2%)	-0.88	0.043	(-0.963 to -0.796)
Total antibody negative or <LLOQ	1475/1890 ^d (78.0%)	-0.86	0.035	(-0.930 to -0.795)
≥ LLOQ	415/1890 ^d (22.0%)	-0.63	0.050	(-0.732 to -0.534)
≤100 nmol/L	370/1890 ^d (19.6%)	-0.64	0.057	(-0.751 to -0.528)
>100 nmol/L	45/1890 ^d (2.4%)	-0.16	0.131	(-0.418 to 0.096)

LLOQ = Lower limit of quantification (3.21 nmol/L); n = number of subjects; N = total number of subjects with available data; SE = standard error.

^a The denominator is number of patients with HbA1c (%) and anti-lixisenatide antibody status data collected on the same date using the simply assay.

^b A fixed-effect meta-analysis method with the inverse of variance as the weight was used for the pooled data of EFC6014, EFC6015, EFC6016, EFC6017, EFC10743, EFC10781, EFC10887 and EFC11321.

^c Based on patients with HbA1c and anti-lixisenatide antibody concentration collected on the same date.

^d Total patients with available data either a negative antibody status or with a measured antibody concentration, plus an available HbA1c measurement, including 173 patients with measured antibody concentration but with missing antibody status. There are also 237 patients with antibody positive status but with missing antibody concentration.

Week 24 value is the last observation carried forward (LOCF) before initiation of rescue therapy on or before week 24.

Antibody Concentration Response Analysis on Efficacy

In several Phase 1 studies, antibody formation was observed as early as 3-5 weeks of treatment. Also, in several Phase 3 studies sponsor conducted anti-lixisenatide antibody measurements at week 4 of the treatment. We conducted an exposure (antibody concentration)-response analysis to evaluate the impact of antibody concentration at week 4 and week 24 on the efficacy at week 24. The main objective of this analysis was to identify patients upfront who are poor responder based on their antibody concentrations at week 4.

Exposure (antibody concentration) response analysis, as seen in the Figure 7, showed a lower response in terms of change from baseline in HbA_{1c} with increasing antibody concentrations at both week 4 and week 24.

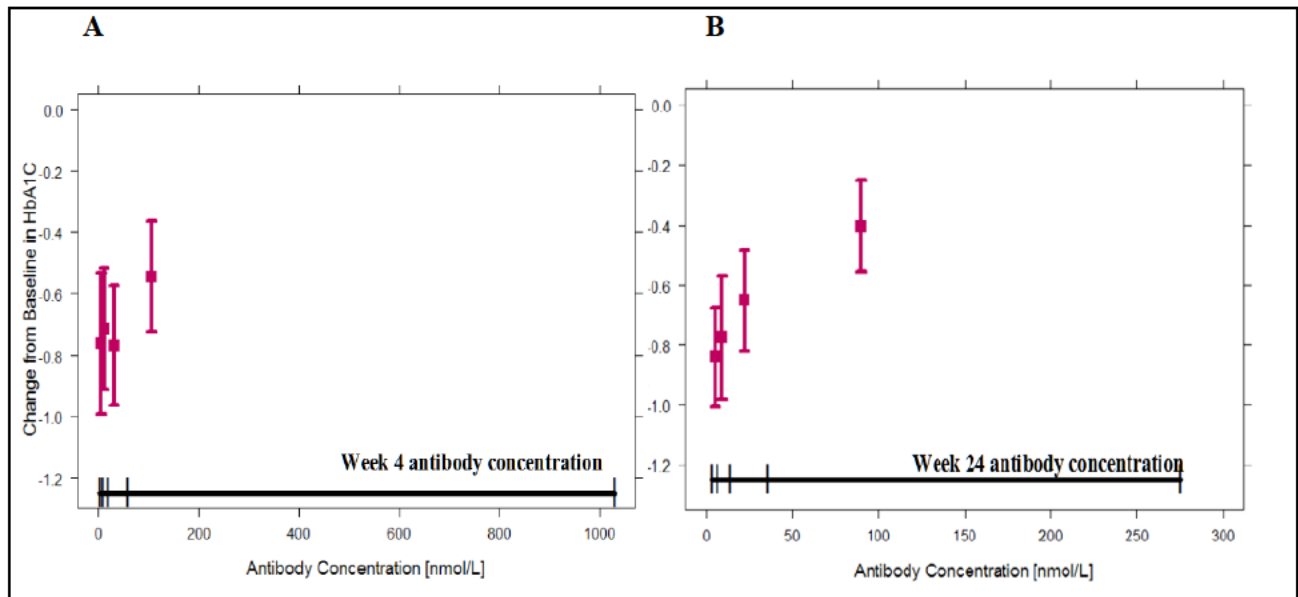
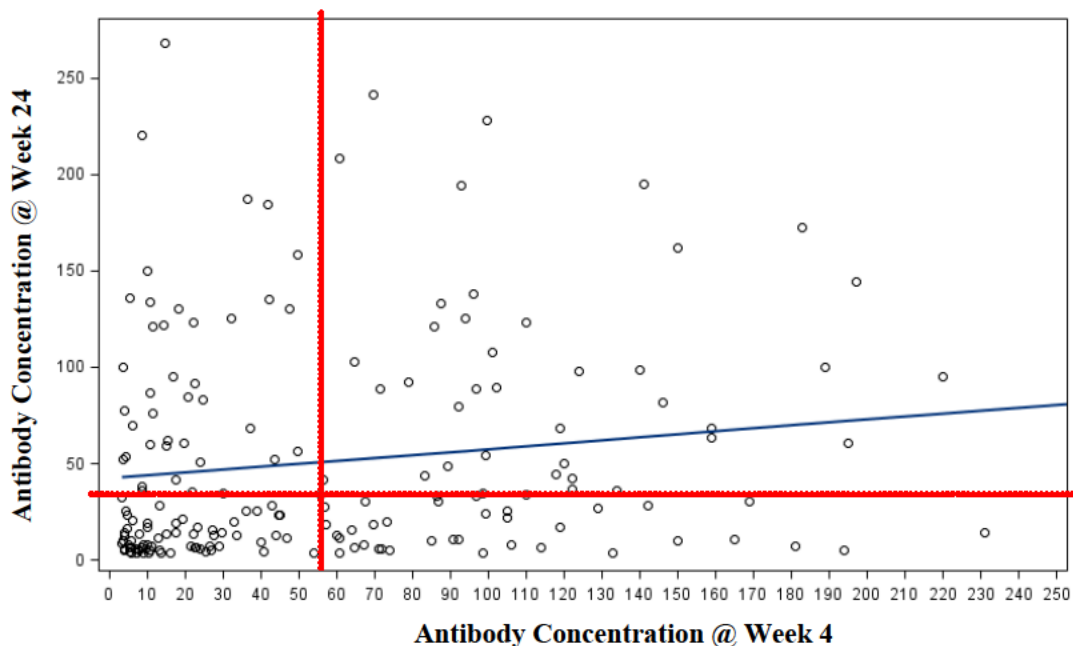


Figure 7: A) Percent change from baseline in HbA1c by antibody quartile at week 4. Based on pooled analysis of Phase 3 trials (N=275). B) Percent change from baseline in HbA1c by antibody concentration quartile at week 24. Based on Sponsor’s data from pooled 8 Phase 3 trials (N=421)

The antibody concentration is divided into four quartiles is denoted by the horizontal black line. Change from baseline in HbA1c is demonstrated as squares at the median of each quartile. The vertical bars represent the mean change from baseline in HbA1c with 95% confidence interval.

We further looked in the relationship between week 4 antibody data to week 24 antibody data (Figure 8). No correlation was observed between week 4 and week 24 antibody data. Since the week 4 antibody data is not predictive of week 24 antibody data, the above analysis of antibody concentration to efficacy is exploratory in nature and no recommendation based on week 4 antibody concentration can be made at this point.



1

Figure 8: Figure showing antibody concentrations at week 4 and at week 24. Red dashed vertical line and horizontal line represents the lower value of antibody concentration of fourth quartile at week 4 and week 24 respectively.

Reviewer's comment: This analysis assumes that the bioanalytical method to detect the antibody concentrations was properly validated.

1.1.4 Is there a need for dose adjustment based on renal function?

No dose adjustment is required for patients with mild or moderate renal function. The sponsor proposed not to use lixisenatide in patients with severe RI because of the very limited subject enrolled in the Phase 3 trials with severe RI. However, given that efficacy of lixisenatide is preserved in patients with moderate RI and that there is no unique safety concerns in this population, lixisenatide can be used with caution in patients with severe RI. The dose of lixisenatide should be restricted to 10 µg QD in patients with severe RI, and should be increased to 20 µg QD only in patients tolerating lixisenatide who require additional glycemic control. Please refer to Clinical Pharmacology review by Dr. Suryanarayana Sista and Clinical Review by Dr. Suchitra Balakrishnan for further details.

Effect of Renal Impairment of Efficacy: Sponsor's subgroup analysis for efficacy based on renal function from the pooled data of nine Phase 3 placebo-controlled studies is shown in Table 5. The LS mean change from baseline in HbA_{1c} was -0.79 for normal renal function subjects, -0.92 for mildly renally impaired subjects, and -0.79 for moderate renally impaired subjects (Table 5). The placebo adjusted difference in LS mean change from baseline in HbA_{1c} was -0.49 for normal renal function subjects, -0.62 for mildly renally impaired subjects, and -0.80 for moderate renally impaired subjects (Table 5). In this pooled analysis there were very limited subjects with moderate (N=33) and none with severe renal function on lixisenatide treatment group. During the review cycle sponsor submitted data from an ongoing CV outcome study (ELIXA) which had a fair amount (N=215) of moderate renally impaired subjects on lixisenatide treatment group. Results on efficacy from ELIXA trial in renally impaired patient

is shown in Table 6. The results of the ELIXA trial also showed that placebo adjusted difference in LS mean change from baseline in HbA_{1c} values for mild to moderate renally impaired patients were numerically greater compared to normal renal function subjects. Thus in terms of efficacy, the renal impairment patients showed better efficacy in pooled analysis and in ELIXA trial.

Table 5: Meta analysis of change in HbA_{1c} (%) from baseline to Week 24 by baseline factors based on the pooled data of 9 Phase 3 Placebocontrolled studies - mITT population

	Placebo (N=1634)			Lixisenatide ^c (N=2857)				
	N	Mean (SD)	LS Mean (SE) ^a	N	Mean (SD)	LS Mean (SE) ^a	Diff in LS Mean (SE) ^b	95% CI ^b
Duration of diabetes (years)								
<10	1032	-0.30 (0.96)	-0.30 (0.035)	1896	-0.82 (0.99)	-0.81 (0.029)	-0.50 (0.034)	(-0.568 to -0.435)
≥10	545	-0.24 (0.87)	-0.27 (0.047)	824	-0.83 (0.91)	-0.81 (0.039)	-0.56 (0.050)	(-0.659 to -0.464)
Baseline renal function status using calculated baseline creatinine clearance (ml/min)								
>80 (normal)	1281	-0.28 (0.94)	-0.29 (0.034)	2234	-0.81 (0.98)	-0.79 (0.028)	-0.49 (0.031)	(-0.554 to -0.432)
≥50 - <=80 (mild renal impairment)	270	-0.29 (0.87)	-0.32 (0.060)	437	-0.87 (0.92)	-0.92 (0.048)	-0.62 (0.069)	(-0.752 to -0.481)
≥30 - <50 (moderate renal impairment)	19	0.15 (0.76)	0.04 (0.218)	33	-0.93 (0.89)	-0.79 (0.210)	-0.80 (0.324)	(-1.434 to -0.163)
<30 (severe renal impairment)	4	-0.30 (0.98)		0				

BMI = Body mass index, Diff = Difference. Studies included: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887 and EFC11321.

a Weighted average of LS means of subgroup analysis from the individual studies with the inverse of variance as the weight

b A fixed-effect meta-analysis method with the inverse of variance as the weight

c Pooled lixisenatide arms for studies EFC6014, EFC6018 and EFC10743 which had 2 lixisenatide regimens.

d Since EFC10887 and EFC11321 were conducted in Asia only, the analysis was performed on the pooled data of other 7 global studies

For a subgroup category, studies with patients in both treatment groups were combined for the meta analysis and LS mean calculation. LS Mean and difference in LS Mean are provided for categories where at least one study had ≥ 5 patients in each treatment group

Week 24 value is the last observation carried forward (LOCF) before initiation of rescue therapy on or before week 24. Patients with both baseline and the Week 24 (week 12 for EFC6018) measurements are included.

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Source: Sponsor's Summary of Clinical Efficacy report Pg 118 Table 17.

Table 6: Analysis of change from baseline in HbA1c at Week 24 (ANCOVA, LOCF) by renal subgroup - ITT population (ELIXA trial)

Renal subgroup Treatment group	Change From Baseline				
	N	Mean (SD)	LS Mean (SE) ^a	Diff in LS Mean (SE) ^{ab}	95% CI ^{ab}
≥15 - <30 ml/min/1.73m² (severe renal impairment)					
Placebo	3	0.47 (0.83)	-0.35 (0.000)	-	-
Lixisenatide	3	-1.10 (1.50)	-0.78 (0.000)	-0.43 (0.000)	(NC to NC)
≥30 - <60 ml/min/1.73m² (moderate renal impairment)					
Placebo	261	-0.01 (1.19)	0.04 (0.082)	-	-
Lixisenatide	215	-0.46 (0.93)	-0.43 (0.085)	-0.46 (0.095)	(-0.652 to -0.278)
≥60 - <90 ml/min/1.73m² (mild renal impairment)					
Placebo	549	-0.18 (0.96)	-0.19 (0.045)	-	-
Lixisenatide	560	-0.58 (1.05)	-0.52 (0.045)	-0.33 (0.054)	(-0.436 to -0.223)
≥90 ml/min/1.73m² (no renal impairment)					
Placebo	197	-0.24 (1.05)	-0.21 (0.078)	-	-
Lixisenatide	220	-0.45 (1.17)	-0.42 (0.074)	-0.21 (0.097)	(-0.396 to -0.017)

^a Analysis of covariance (ANCOVA) model with treatment group and region as fixed effects and baseline HbA1c value as a covariate.

^b Difference in LS Mean between lixisenatide and placebo.

Week 24 value is the last observation carried forward (LOCF) before Week 24. Patients with both baseline and the Week 24 measurements are included.

Randomization data received: 25JUL2012 / CRF data received: 25JUL2012

Source: Sponsor's Summary of Clinical Efficacy report Pg 118 Table 17.

Effect of Renal Impairment on Safety: Subgroup analysis for GI related side effects based on renal function on the pooled data of nine Phase 3 placebo-controlled studies is shown in Table 7. Safety results based on renal function indicates that more GI related side effects were observed in mild and moderate renally impaired patients as compared to normal. The increased number of GI related side effects could be due to higher PK exposure in renally impaired patients. There were no other unique safety concerns observed in patients with moderate renal impairment. No dosing adjustment is recommended in patients with moderate RI; however, use with caution is recommended because of general concerns of dehydration leading to acute renal failures with this class of drugs. Please refer to the clinical review by Dr. Suchitra Balakrishnan for complete details of the results from efficacy and safety trial patients with moderate RI.

The sponsor proposed not to use lixisenatide in patients with severe RI because of the very limited subject enrolled in the Phase 3 trials with severe RI. However, given that efficacy of lixisenatide is preserved in patients with moderate RI and that there is no unique safety concerns in this population, lixisenatide can be used with caution in patients with severe RI. The dose of lixisenatide should be restricted to 10 µg QD in patients with severe RI, and should be increased to 20 µg QD only in patients tolerating lixisenatide who require additional glycemic control. The recommendation for 10 µg QD dose in patients with severe RI is based on exposure matching. Please refer to Clinical Pharmacology review by Dr. Suryanarayana Sista and Clinical Review by Dr. Suchitra Balakrishnan for further details.

Table 7: Analysis of change from baseline in HbA1c at Week 24 (ANCOVA, LOCF) by renal subgroup - ITT population (ELIXA trial)

	> 80 mL/min (normal)		50 to 80 mL/min (mild)		30 to < 50 mL/min (moderate)		< 30 mL/min (severe)	
	Placebo Lixisenatide		Placebo Lixisenatide		Placebo Lixisenatide		Placebo Lixisenatide	
SYSTEM ORGAN CLASS	(N=1332) (N=2337)		(N=278)	(N=478)	(N=22)	(N=38)	(N=4)	(N=0)
GASTROINTESTINAL DISORDERS n(%)	264 (19.8%)	899 (38.5%)	41 (14.7%)	220 (46.0%)	3 (13.6%)	21 (55.3%)	0	0

Source: Sponsor's Integrates Summary of Safety report Pg 202.

Main treatment period: 12 weeks for EFC6018 and 24 weeks for other studies

Studies included: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887 and EFC11321

Reviewers Comments: Higher number of patients in mild and moderate renally grouped patients experienced GI related side effects. Due to short half-life of this drug, the trough samples collected in the Phase 3 trials were below the limit of quantification and thus no exposure-response relationship could be done with these phase 3 trials. However, from the dedicated Phase 1 renal impairment study, it is known that mild and moderate subjects have higher exposure compared to subjects with normal renal function. Hence, more GI related side effect seen in mild and moderate group could perhaps be due to higher PK exposure in these subjects.

Effect of Renal Impairment on Pharmacokinetics of Lixisenatide:

In dedicated Phase 1 trial, patients with mild moderate and severe renal impairment showed 48%, 65%, and 123% higher AUCs, respectively, as compared to subjects with normal renal function. Please refer to Clinical Pharmacology review by Dr. Suryanarayana Sista for further details.

Similarly, in population PK analysis, creatinine clearance was found to be a significant covariate for lixisenatide clearance. Based on population PK analysis there is an increase in lixisenatide clearance with increasing creatinine clearance (Figures 12 A and B). Although creatinine clearance is identified as a covariate, the inclusion of creatinine clearance did not reduce the inter-individual variability on clearance. Therefore, the metrics for change in exposure in different renal impairment categories are primarily based on dedicated phase 1 trial.

1.1.5 Is there a need for dose adjustment for age, gender, race or bodyweight based on the pharmacokinetics of lixisenatide?

Based on the population PK analysis, no dose adjustment is required based on age, gender, race, and body weight. Based on the final model, no systematic trend was observed between inter-individual variability on clearance and body weight, age, gender or race (Figure 9). It is worthwhile to note the sponsor conducted dedicated Phase 1 trials to see the impact of age and race on the pharmacokinetics of lixisenatide. Population PK analysis to support labeling claims related to age and race is supportive to these dedicated Phase 1 trials.

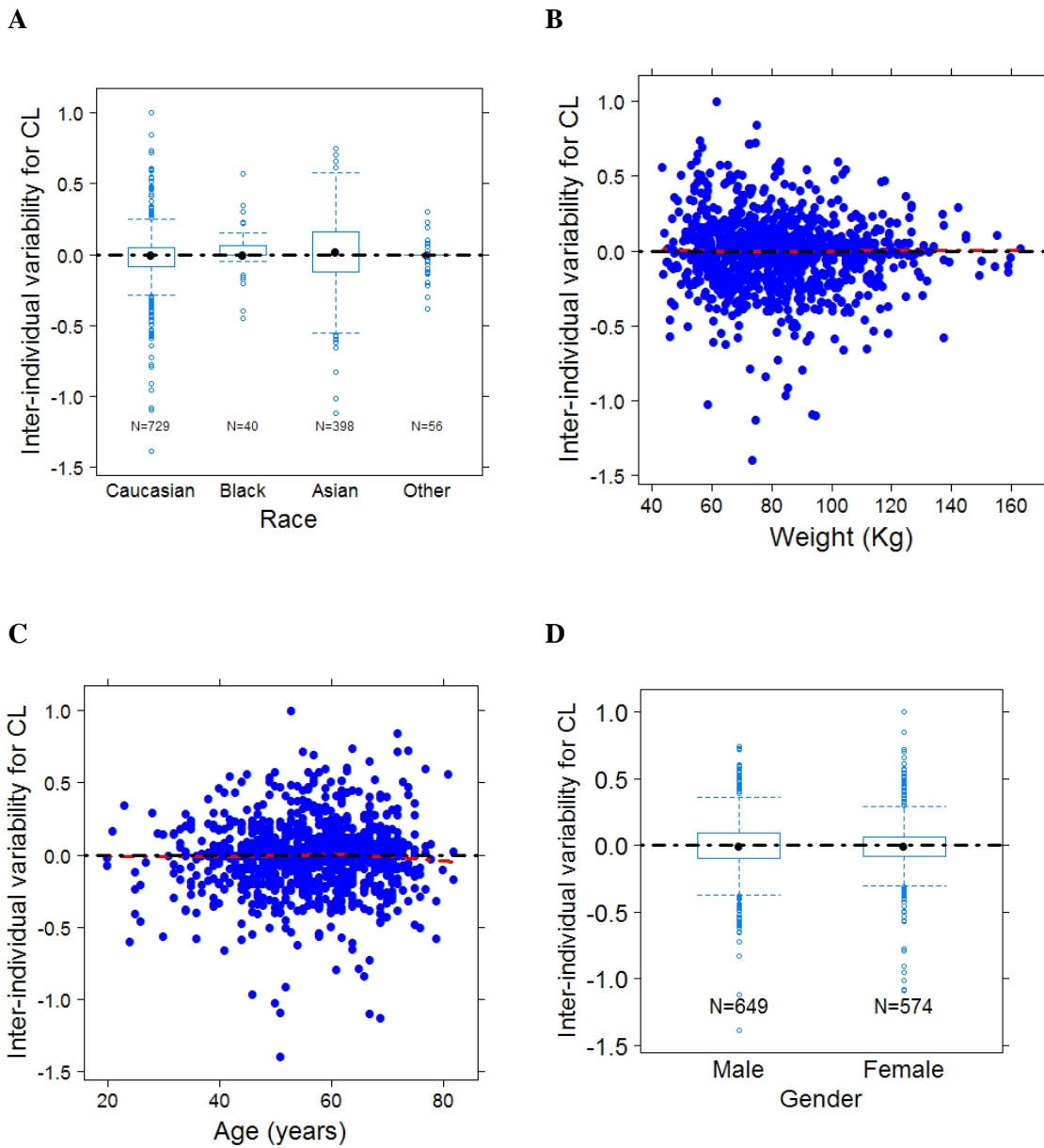


Figure 9: Based on Final Model, Inter-individual variability on clearance vs A) Race, B) Body Weight, C) Age, D) Gender

1.2 Recommendations

Division of Pharmacometrics finds the NDA approvable from a clinical pharmacology perspective.

1.3 Labeling Recommendations

The following are the labeling recommendations relevant to clinical pharmacology for NDA 204961. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

Effects of Age, Body weight, Gender and Race

(b) (4)

(b) (4)

Reviewer's comments:

Proposed labeling claim by the Sponsor that

(b) (4)

is acceptable. However, details of the population PK analysis have been removed to keep the label concise.

2 Results of Sponsor's Analysis

2.1 Population PK Analysis

Sponsor performed population PK modeling utilizing data from 7 clinical studies that includes two Phase 1 (BDR6864 and POP6053), two Phase 2 study in T2DM subjects (PDY6797 and DRI6012), and three Phase 3 trials in T2DM subjects (EFC6018, EFC6015 and EFC10887). Primary objective of the population PK analysis was to identify subject characteristics (age, race, gender, renal function, body weight etc.) that are predictive of variability in the pharmacokinetic parameters of lixisenatide and therefore may require dose adjustments.

2.1.1 Methods

PK data was collected from a total 1223 subjects (a total of approx 9600 plasma total lixisenatide concentrations), measured in the absence of anti-lixisenatide antibodies, from 75 healthy subjects and 1148 patients with T2DM. Data consisted of two Phase 1 (BDR6864 and POP6053), two Phase 2 study in T2DM subjects (PDY6797 and DRI6012), and three Phase 3 trials in T2DM subjects (EFC6018, EFC6015 and EFC10887). In these trials lixisenatide was administered as either single subcutaneous (n=75), or multiple subcutaneous doses (n=1148) ranging from scheduled 5 to 30 µg and was given QD or BID for up to 19 months. Description of the studies with other relevant information is provided in Table 8.

Table 8: Studies Used for the Population PK Model

Study no.	Study population	Doses ^a	Pharmacokinetic sampling times
Phase 1 studies			
BDR6864	Overweight and obese, otherwise healthy	10 µg	intensive 3d
POP6053	Healthy with either normal renal function or mild, moderate, or severe renal impairment	5 µg	intensive 3d
Phase 2 studies			
PDY6797	T2DM	Starting doses of 5 µg or 10 µg, then weekly dose escalation in 5 µg increments from 5 or 10 µg QD or BID up to 30 µg QD or BID	intensive 2d
DRI6012	T2DM	QD or BID 5, 10, 20, or 30 µg for 13 weeks; for dose levels 20 and 30 µg: Starting dose: 5 µg for QD or BID 5 µg, to be increased in weekly increments of 5 µg	intensive over 4 hours after 13 weeks
Phase 3 studies			
EFC6018	T2DM	20 µg QD	sparse ^b
EFC10887	Asian T2DM	20 µg QD	sparse ^c
EFC6015	T2DM	20 µg QD	sparse ^d

Source: Sponsor's Population PK Report, Page 357

A one-compartment pharmacokinetic model with first-order absorption was used to describe lixisenatide pharmacokinetics, using NONMEM Version 7.2 software. All runs were performed using the first-order conditional estimation method with η - ϵ interaction. A combined additive and proportional statistical error model (in the log domain) was evaluated.

PK data were fitted using NONMEM Version 7.2 ((ICON Development Solutions, Ellicott City, MD, USA). ADVAN2 subroutine and the first-order conditional estimation method with interaction (FOCEI) were used after logarithmic data transformation. Graphical data visualization, evaluation of NONMEM outputs, construction of goodness-of-fit plots and graphical model comparisons were conducted using R, version 2.12.1. Lixisenatide concentration data obtained in the presence of anti-lixisenatide antibodies were not considered for PopPK analysis. The concentrations were logarithmically transformed prior to modeling.

The PPK model was developed in 3 stages. First, a base model was developed to describe the PK without consideration of covariate effects. Second, a full-covariate model was developed by incorporating the effects of all potentially significant covariate-parameter relationships, and lastly the final model was developed by retaining only the statistically significant covariate-parameter relationships by step-wise backward elimination. Model building and covariate assessments were conducted using standard methods. Covariate relationships were considered only on parameters on which inter-individual (IIV) and/or inter-occasion variability (IOV) were significant. The final model for the PK database was evaluated for performance using visual predictive check (VPC) and quantitative predictive check evaluation.

2.1.2 Final Model

To arrive at the final model, the full model was subjected to a step-wise backward elimination procedure. The pharmacokinetics of lixisenatide following subcutaneous injection was best described by a one-compartment model, with a first order absorption (k_a), with IIV and IOV on apparent clearance (CL/F), apparent volume of distribution (V/F) and mean absorption time ($\text{MAT}=1/k_a$), and with a combined additive and proportional residual error (in the log domain).

After the backwards elimination procedure was completed, 3 covariate-parameter relationships were retained in the final model: cCrCL on CL/F, and body weight on V/F and dose on MAT. The IIV parameters of the base model were specified by a lognormal distribution. The NONMEM output for the final model is presented in Table 9.

Table 9: Parameter Estimates of Final Model (Final)

Structural model:			
$CL/F = \theta_{CL/F} \cdot (1 + \theta_{CLCR\_CL} \cdot (CLCR - 6.2 \text{ L/h})) \cdot e^{\eta_{CL_{IIV}} + \eta_{CL_{IOV}}}$			
$V/F = \theta_{V/F} \cdot \left(\frac{WT}{82.1 \text{ kg}}\right)^{\theta_{WT\_V}} \cdot e^{\eta_{V_{IIV}} + \eta_{V_{IOV}}}$			
$MAT = \theta_{MAT} \cdot \left(\frac{Dose}{15 \text{ mg}}\right)^{\theta_{Dose\_MAT}} \cdot e^{\eta_{MAT_{IIV}}}$			
Residual random effect model:			
$\log(y(t)) = \log(f(t) + m) + \frac{f(t)}{f(t)+m} \cdot e_1(t) + \frac{m}{f(t)+m} \cdot e_2(t)$			
Parameter ^a	Estimate	95% CI	Description
CL/F (L/h)	38.6	36.6-40.7	Apparent clearance
V/F (L)	41.2	37.5-45.3	Apparent volume of distribution
MAT (h)	3.25	3.06-3.47	Mean absorption time
θ_{CLCR_CL}	0.099	0.079-0.119	fractional change of population CL/F per L/h deviation from median creatinine clearance, CLCR
θ_{WT_V}	1.56	1.32-1.79	Effect of WT on V/F
θ_{Dose_MAT}	0.236	0.177-0.296	Effect of Dose on MAT
IIV in CL/F (%CV)	40.3	33.1-46.4	Inter-individual variability in CL/F
IIV in V/F (%CV)	30.3	12.1-41.1	Inter-individual variability in V/F
IIV in MAT (%CV)	30.0	24.2-34.8	Inter-individual variability in MAT
IOV in CL/F (%CV)	44.9	40.3-49.1	Inter-occasion variability in CL/F
IOV in V/F (%CV)	59.3	50.1-67.2	Inter-occasion variability in V/F
Proportional residual variability (%CV)	14.2	12.7-15.6	
Additive residual variability (SD ng/L)	1.70	1.35-2.05	
$cor(\eta_{CL_{IIV}}, \eta_{V_{IIV}})$	-0.029		Correlation between IIV for CL/F and V/F
$cor(\eta_{CL_{IOV}}, \eta_{V_{IOV}})$	-0.058		Correlation between IOV for CL/F and V/F

^a IIV and IOV estimates (%CV) are in log domain.

Source: Sponsors Population PK Report, Pages 44

Figure 10 shows basic goodness of fit plots for the Sponsor’s final model. Figure 11 show visual predictive check (VPC) of the final model.

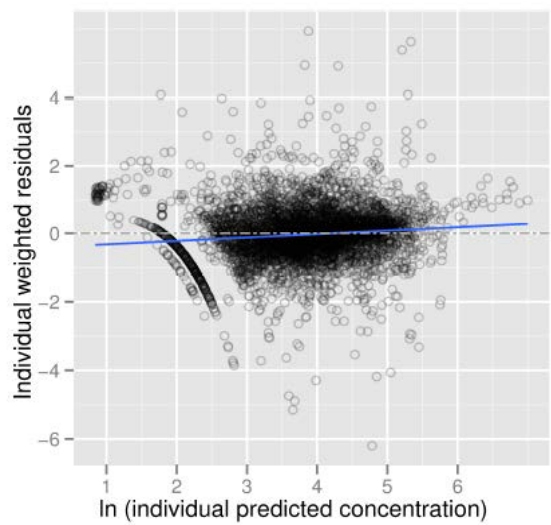
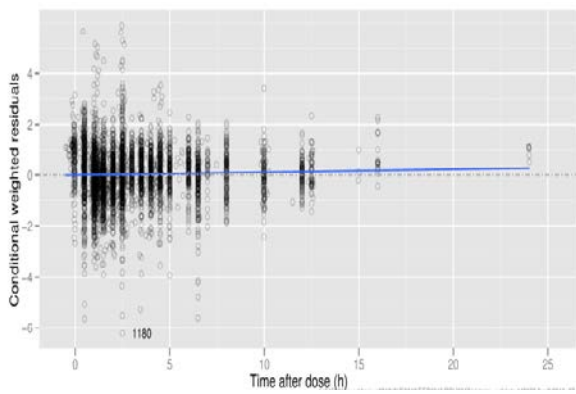
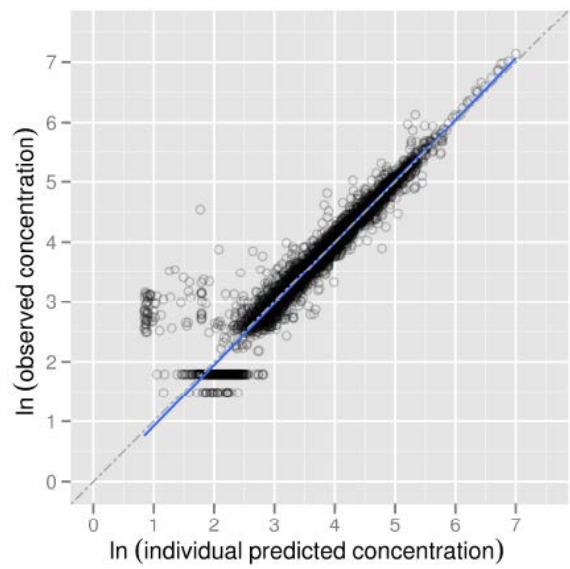
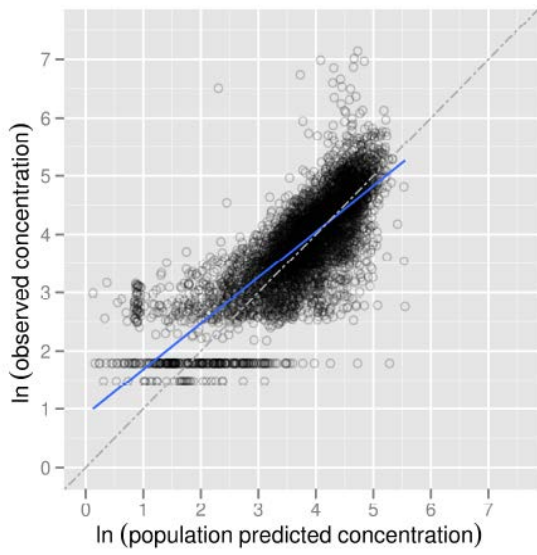


Figure 10: Basic goodness of fit plots for the Sponsor's final model

Source : Sponsors Population PK Report, Pages 174

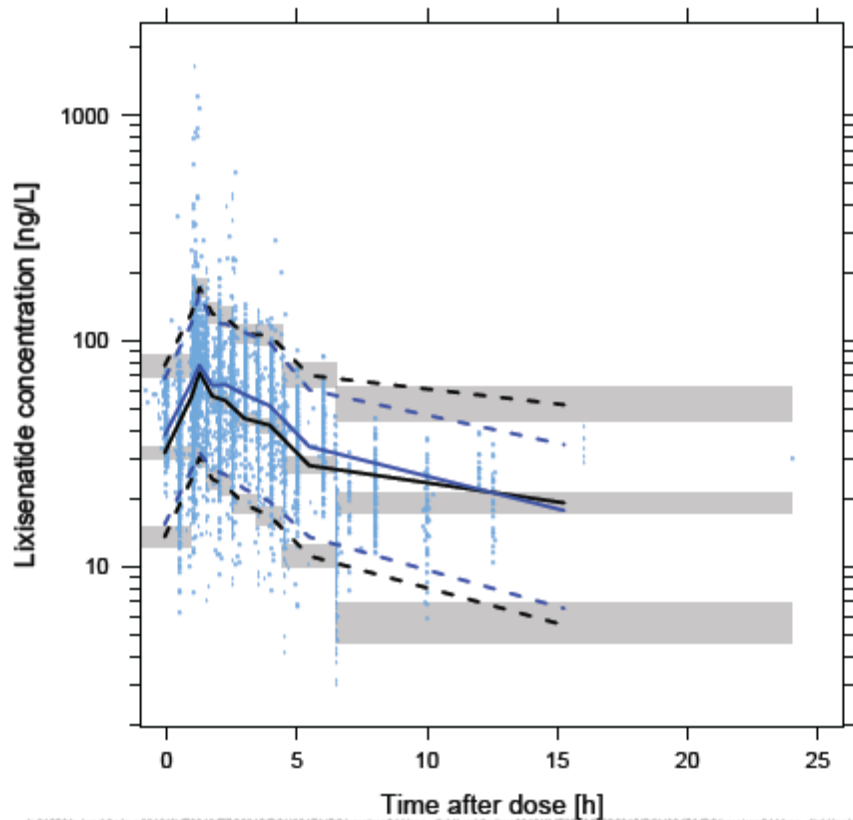


Figure 11 : VPC for lixisenatide plasma concentrations versus time after dose, based on final model (fit .449628). The light grey shaded areas indicate the simulation-based 90% confidence interval for the model-predicted 5%, 50% and 95% percentiles. The blue lines indicate the observed 5%, 50% and 95% percentiles. The black lines connect the median of the model-predicted percentiles. The light blue circles are the prediction-corrected observations.

Source : Sponsors Population PK Report, Pages 52

2.1.2.1 Lixisenatide Covariate Effects

After incorporating the covariates into the basic model, the IIV on CL/F increased from 35.5 % to 40.3 %, and the IIV for MAT only decreased from 33.2% to 30.0%, whereas the IIV for V/F clearly decreased from 61.4% to 30.3% (all values in log domain). Thus, there were essentially no relevant reductions in the IIV for CL/F and MAT by incorporating covariates.

Derived steady-state PK parameter from the final population pharmacokinetic model, fit 449628, normalized to a subject of 82.1 kg body weight and creatinine clearance of 6.2 L/h receiving 20 µg lixisenatide is presented in Table 9. Derived steady-state PK parameter from the final population pharmacokinetic model, fit .449628, normalized to a subject of 82.1 kg body weight and creatinine clearance of 6.2 L/h receiving 20 µg lixisenatide, stratified by gender is presented in Table 9.

Table 9: Derived steady-state PK parameter from the final population pharmacokinetic model, fit .449628, normalized to a subject of 82.1 kg body weight and creatinine clearance of 6.2 L/h receiving 20 µg lixisenatide

Variable	n	mean	sd	CV%	median	min	max
C _{max} (ng/L)	1223	95.2	24.3	25.5	92.4	33.2	367.6
t _{max} (h)	1223	1.78	0.22	12.28	1.77	0.89	3.29
AUC (ng.h/L)	1223	534	131	24	518	198	1987
C _{avg} (ng/L)	1223	22.2	5.4	24.5	21.6	8.2	82.8
R _{ac}	1223	1.00	0.00	0.01	1.00	1.00	1.00
k _a (h ⁻¹)	1223	0.31	0.05	16.64	0.31	0.15	0.91
k _e (h ⁻¹)	1223	0.95	0.20	21.50	0.94	0.26	2.47
t _{1/2z} (h)	1223	2.26	0.31	13.73	2.26	0.76	4.54

Stratified by Gender								
Variable	SEX	n	mean	sd	CV%	median	min	max
C _{max} (ng/L)	male	649	95.3	24.5	25.8	92.4	46.0	353.6
	female	574	95.1	24.0	25.3	92.4	33.2	367.6
t _{max} (h)	male	649	1.77	0.23	12.92	1.77	0.89	2.94
	female	574	1.78	0.20	11.52	1.77	1.09	3.29
AUC (ng.h/L)	male	649	535	133	25	518	254	1987
	female	574	533	128	24	518	198	1523
C _{avg} (ng/L)	male	649	22.3	5.6	24.9	21.6	10.6	82.8
	female	574	22.2	5.3	24.0	21.6	8.2	63.4
R _{ac}	male	649	1.00	0.00	0.00	1.00	1.00	1.00
	female	574	1.00	0.00	0.01	1.00	1.00	1.00
k _a (h ⁻¹)	male	649	0.31	0.06	18.60	0.31	0.15	0.91
	female	574	0.31	0.04	14.11	0.31	0.20	0.70
k _e (h ⁻¹)	male	649	0.96	0.21	21.48	0.94	0.39	1.94
	female	574	0.95	0.20	21.53	0.94	0.26	2.47
t _{1/2z} (h)	male	649	2.27	0.33	14.60	2.26	0.76	4.54
	female	574	2.25	0.29	12.68	2.26	1.08	3.48

Source: Sponsors Population PK Report, Pages 48

2.2 Sponsor's Conclusions

- The pharmacokinetics of lixisenatide following subcutaneous injection was best described by a one-compartment model, with a first order absorption (k_a), with IIV and IOV on apparent clearance (CL/F), apparent volume of distribution (V/F) and mean absorption time (MAT=1/ k_a), and with a combined additive and proportional residual error (in the log domain).

- Among the covariates tested, *CLCR* was the most important covariate for explaining the IIV of total lixisenatide CL/F; dose (tested in the range of 5 µg QD to 30 µg BID) was the most important covariate for explaining the IIV of the MAT.
- Body weight had a major effect on the IIV of V/F. No isolated effect of gender, race, or age was identified.
- The remaining IIV (not explained by covariate effects) was 40.3%, 30.3% and 30.0% on CL/F, V/F and MAT, respectively (in log domain). The IOV (44.9% to 59.3%) was higher than the IIV, suggesting a limited potential for dose optimization.

Reviewer's comments on Sponsor's Population PK Analysis:

- *Sponsor's population PK analysis is generally adequate and acceptable for the purpose of labeling recommendations.*
- *During base model development sponsor excluded some observations if log-transformed observed concentrations exceeded the IPRED by more than 2. Sponsor did not provide any adequate rationale for this exclusion of observation. The excluded observations were only about 3% of the total samples used in the analysis. Thus, it is assumed that these exclusions have very little impact on the overall analysis.*
- *Based on population PK analysis, creatinine clearance was identified as significant covariate for clearance and body weight was identified as significant covariate affecting volume of distribution of lixisenatide. Although creatinine clearance is identified as a covariate, the inclusion of creatinine clearance did not reduce the inter-individual variability on clearance. The conclusions regarding dose adjustment based on renal function will be derived based on dedicated phase 1 trial.*
- *Sponsor's conclusion that no dose adjustment based on age, gender, body weight and race is acceptable. See reviewer's independent analysis in section 3.3.*
- *Sponsor conducted dedicated Phase 1 trials to see the impact of age and race on the pharmacokinetics of lixisenatide. Population PK analysis is supportive to these dedicated Phase 1 trials.*

3 Results of Reviewer's Analysis

3.1 Objectives

The primary objective was to confirm sponsor's claim that there are no clinically meaningful effects of gender, race, body weight, and creatinine clearance on lixisenatide pharmacokinetics.

3.2 Methods

3.2.1 Data Sets

Data set used are summarized in Table

Table : Analysis Data Set

Study Number	Name	Link to EDR
DR6864 POP6053 PDY6797 DRI6012 EFC6018, EFC6015 EFC10887	Final.xpt (For Final Model Run) Total.xpt (For Base Model Run)	\\Cdsub1\evsprod\NDA204961\0000\m5\datasets\poh0347\analysis\legacy\datasets\

3.2.2 Software

NONMEM version 7.2 and R V2.10.1 were used for reviewer's analysis.

3.3 Results

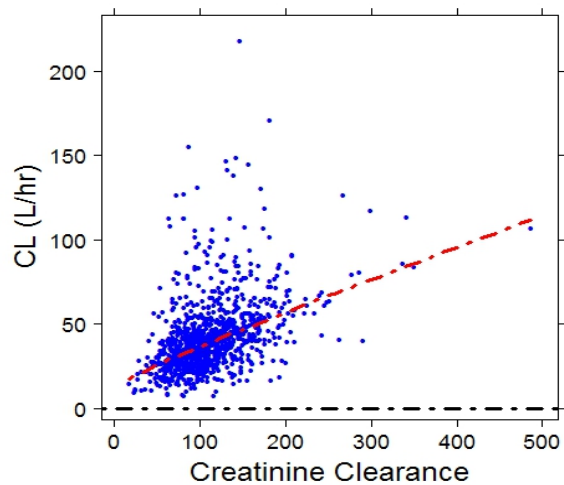
There is an increase in lixisenatide clearance with increasing creatinine clearance (Figures 12 A and B). The mean clearance in subjects with severe, moderate, and mild renal impairment is 65%, 40%, and 22% lower, respectively, than that of normal renal function subjects. After inclusion of creatinine clearance in sponsor's final model, no systematic trend between inter-individual variability on clearance and creatinine clearance is observed (Figure 12C).

There is a trend for increasing lixisenatide clearance with increase in body weight (Figure 13A). However, body weight was found to be highly correlated to cCrCL and thus after inclusion of creatinine clearance in the final model no systematic trend between inter-individual variability on clearance and body weight as observed in Figure 13B.

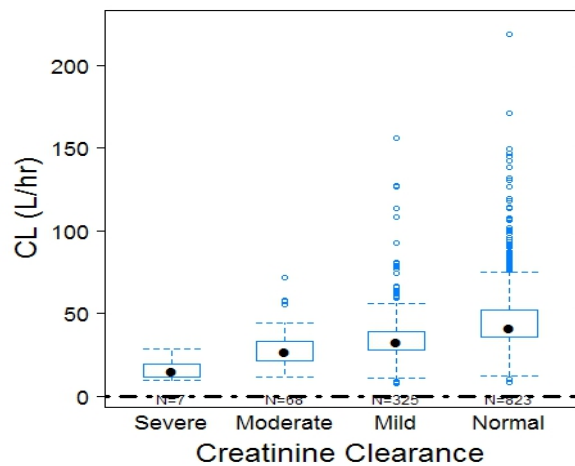
There is also a trend for decrease in clearance with increasing age (Figure 14A and 14B). Age was found to be highly correlated to cCrCL and thus after inclusion of creatinine clearance in the final model resulted in no systematic trend between inter-individual variability on clearance and age (Figure 14C).

Gender and race do not significantly affect the clearance of lixisenatide. Figure 15 and Figure 16 show that the inter-individual variability in clearance cannot be explained by gender and race respectively.

A



B



C

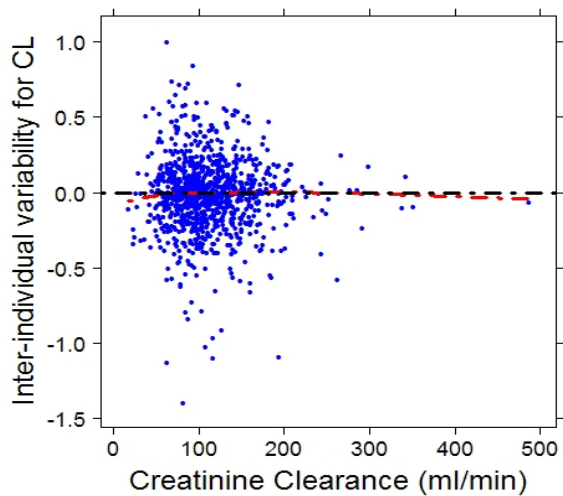
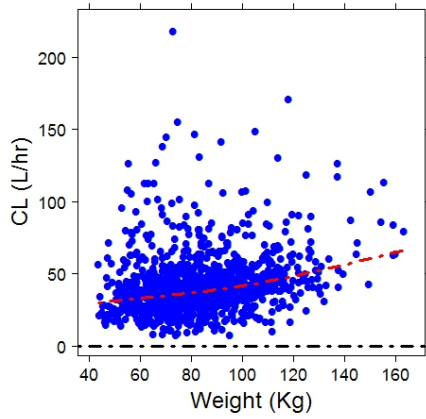


Figure 12: A) Scatter plot of clearance vs. creatinine clearance, B) Boxplot of clearance vs. creatinine clearance and C) Inter-individual variability on clearance vs. creatinine clearance

A



B

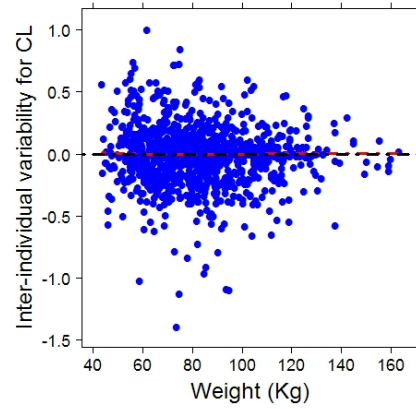
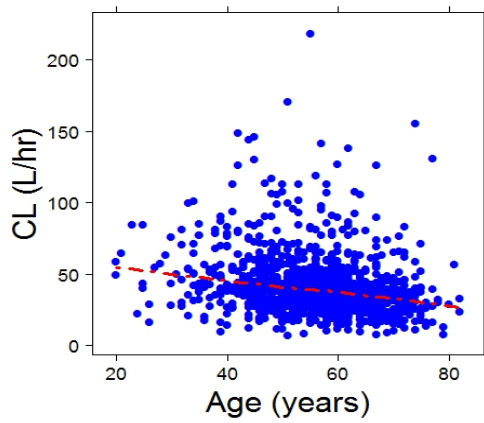
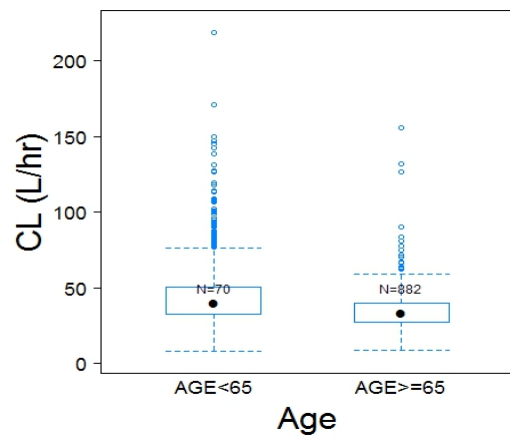


Figure 13: A) Scatter plot for clearance vs. weight B) Inter-individual variability on clearance vs. weight

A



B



C

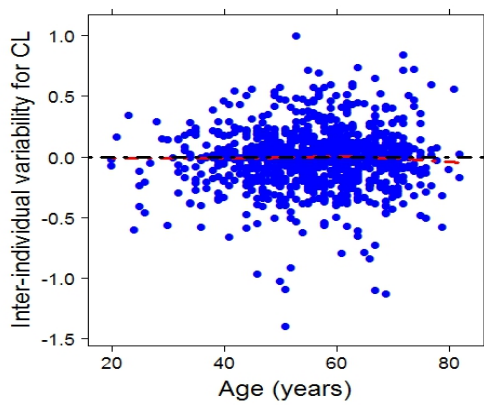


Figure 14: A) Scatter plot for clearance vs. age B) Boxplot of clearance vs. age and C) Inter-individual variability on clearance vs. age

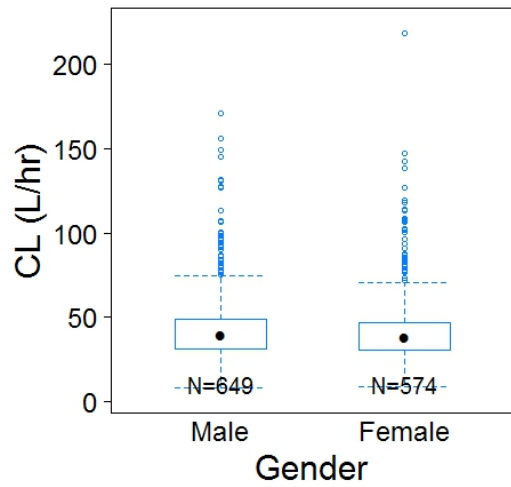
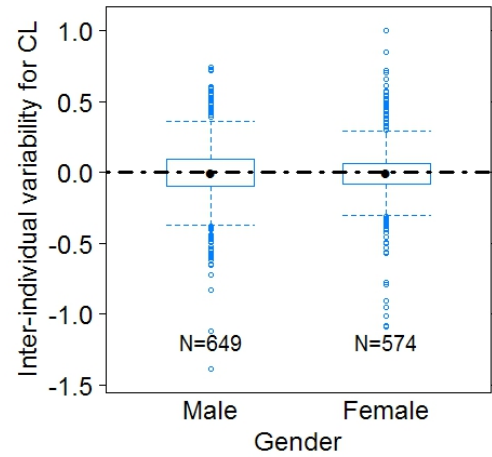
A**B**

Figure 15: A) Clearance and B) Inter-individual variability on clearance vs. gender

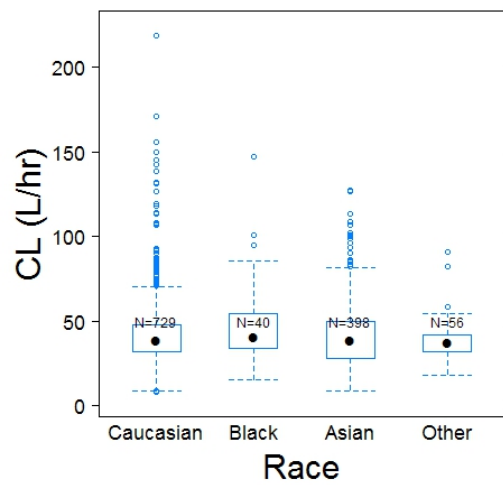
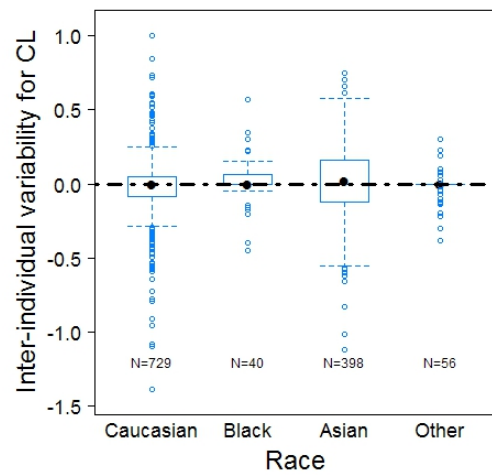
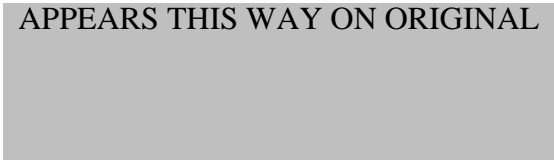
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Figure 16: A) Clearance and B) Inter-individual variability on clearance vs. race.

4.2 IRT Review of TQTc Study

APPEARS THIS WAY ON ORIGINAL



**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

IND	62724
Generic Name	AVE0010; lixisenatide
Sponsor	Sanofi Aventis
Indication	Metabolic Control of Type II Diabetes
Dosage Form	Solution for Subcutaneous Periumbilical Injection,
Drug Class	GLP-1 receptor agonist
Therapeutic Dosing Regimen	20 µg q.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Single dose: 40 µg Multiple dose: above 30 µg b.i.d. after titration
Submission Number and Date	SDN 337 April 17, 2012
Review Division	DMEP / HFD 510

Note: Any text in the review with a light background or quoted should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The largest upper bounds of the 2-sided 90% CI for the mean difference between lixisenatide (20 µg q.d. and 30 µg b.i.d.) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta QTcF$ for moxifloxacin was higher than 5 ms, and the moxifloxacin profile over time is demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, double-blind, double-dummy, multiple dose, placebo-controlled parallel study, 91 healthy subjects received lixisenatide 20 µg once daily, lixisenatide 30 µg twice daily, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for AVE0010 (20 µg and 30 µg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Lixisenatide 20 µg q.d.	3	4.6	(1.8, 7.5)
Lixisenatide 30 µg b.i.d.	3	5.5	(2.6, 8.3)
Moxifloxacin 400 mg*	3	12.0	(8.5, 15.4)

* Multiple endpoint adjustment of 3 time points was applied.

The selection of 20-µg q.d. dose as the therapeutic dose appears to be reasonable. The suprathreshold dose (30 µg b.i.d.) represents the highest dose tested. The overall exposure as well as the variability of the pharmacokinetic parameters increased largely in the antibody-positive subjects. The pharmacokinetic data in this study covered a wide range of lixisenatide exposure with mean values of C_{max} up to 209 pg/mL and AUClast up to 979 pg*h/mL in antibody-negative subjects, and C_{max} up to 945 pg/mL and AUClast up to 12500 pg*h/mL in antibody-positive subjects. The mean C_{max} and AUC of lixisenatide was approximately 40% higher at 30 µg b.i.d. than at 20 µg q.d. in antibody-negative subjects or antibody-positive subjects. Significant but shallow exposure-response relationship was observed. However, there is no substantial QT prolongation in the exposure range at the therapeutic dose of 20 µg q.d. and the suprathreshold dose of 30 µg b.i.d.

Lixisenatide exposure is significantly increased in patients with severe renal impairment. However, the increase in lixisenatide exposure (e.g., C_{max}) was not reported (Highlights of Clinical Pharmacology). Whether or not suprathreshold dose is adequate to cover the worst case high exposure clinical scenario will depend on the exposure increase in severe renal impairment.

2 BACKGROUND

2.1 PRODUCT INFORMATION

Lixisenatide is a GLP-1 receptor agonist.

2.2 MARKET APPROVAL STATUS

Lixisenatide is not approved for marketing in any country.

2.3 PRECLINICAL INFORMATION

From IB (14 March 2012)

At a concentration of 0.57 µg/mL, lixisenatide had no effect on resting membrane potential and action potential parameters in electrically stimulated rabbit Purkinje fibers (DSE2005-0098). A moderate and dose-dependent block of delayed rectified potassium currents by lixisenatide was observed in Chinese hamster ovary cells stably expressing

the human ether-à-go-go related gene channel; maximum inhibition was 37.3% at the highest concentration tested (30 µg/mL) (DSE2003-1521). It was not possible to test the effect of lixisenatide up to a concentration of 100 µg/mL, as initially intended, since at any higher concentration the compound disrupted the seal between cell and electrode. The reason for this phenomenon is unknown, but might be due to a surface-active property of lixisenatide. However, the lowest concentration tested was four orders of magnitude higher than C_{max} in clinical studies at 20 µg q.d., indicating a large exposure margin.

In conscious rats, IV administration of lixisenatide increased mean arterial pressure by approximately 25% at 50 µg/kg, with no further increase with cumulative dosing (00-127). This effect on mean arterial pressure is described to be rat-specific for GLP-1-agonists in the literature.

In anesthetized Beagle dogs, no effect on blood pressure and other cardiovascular parameters (ECG, femoral artery blood flow and resistance) was seen (DSE2004-1182). In addition, no effects significantly different from controls regarding respiratory parameters have been observed after lixisenatide doses of up to 10 µg/kg IV.

In anesthetized dogs, a 30-minute infusion of lixisenatide at 10 µg/kg induced a moderate but statistically significant decrease in serum glucose concentration, reaching a maximum of 1.43 ± 0.22 mmol/L at the end of infusion, a slight but significant increase in heart rate at mid infusion and at the end of infusion, reaching a maximum of +5 ± 1.6 bpm at mid infusion, and a marginal but significant decrease of PQ interval duration at mid infusion related to heart rate increase and reaching a maximum of 2 ± 0.9 ms. No effects on potassium concentration, body temperature, QRS complex duration and on QT (corrected or not) interval duration were observed (CRV0345).

The combination lixisenatide followed with insulin glargine induced a significant decrease in serum glucose concentration, reaching a maximum of 3.78 ± 0.32 mmol/L at 30 minutes after administration, a significant decrease in serum potassium concentration, reaching a maximum of 1.1 ± 0.25 mmol/L at 15 minutes after administration, a significant increase in heart rate, reaching a maximum of +16 ± 5.3 bpm at 45 minutes post dosing, reversible ECG morphology modifications up to 60 minutes post injection (minor ST segment elevation, T wave morphology and amplitude modifications), and an increase in QT interval duration (corrected or not), reaching a maximum of +15 ± 4.5 ms, + 26 ± 3.5 ms and +19 ± 3.2 ms for QT, QTcF, and QT interval corrected according to van de Water formula (QTcW) respectively, significant at 15 minutes. The effects on QTcF and QTcW remained significant from 15 to 90 and 15 to 60 min post dosing, respectively. No effect on PQ interval duration QRS complex duration occurred (CVR0345). These effects are probably linked to decreased potassium serum concentrations caused by insulin glargine.

Reviewer's comments: Lixisenatide inhibits hERG currents with low affinity. The combination of lixisenatide and insulin decreases serum glucose concentration, potassium concentration, increases heart rate and QTc duration.

2.4 PREVIOUS CLINICAL EXPERIENCE

From IB (14 March 2012)

At the cut-off for this document, 960 subjects and patients have been treated in 9 completed studies, and 735 thereof have been exposed to AVE0010. Safety in T2DM has been assessed in a total of 754 patients with 573 exposed to AVE0010 (555 with repeated-dose regimen).

A thorough QT/QTc study (TES6865) investigated the potential for delayed ventricular repolarization (QT interval prolongation) after multiple-doses of lixisenatide at the maintenance dose of 20 µg q.d. and at a supratherapeutic dose of 30 µg b.i.d.. At both doses of lixisenatide, there were no relevant or statistically significant mean increases in the QTcF or PR interval. There was no relevant change in heart rate in the 20 µg q.d. group, but at the supratherapeutic dose, the mean heart rate versus placebo increased by 4.73 beats per minute (bpm). A total of 91 subjects enrolled in the study were evaluated for safety. Two subjects discontinued the study due to an adverse event (1 due to urticaria in the 30 µg b.i.d. and 1 due to pruritic rash in the 20 µg q.d. regimens of AVE0010 on Day 14 and Day 22, respectively). No deaths or serious adverse events were reported during the study.

A central reading of ECGs was also conducted in the Phase 3 Study EFC6018 in which 239 patients were exposed to lixisenatide. At the maintenance dose of 20 µg q.d., no adverse findings on QTcF (-0.93 ms versus 2.63 ms for placebo) or heart rate (-0.6 bpm versus 1.3 bpm for placebo) were detected. In this study, 139 (55%) patients were antibody-positive. In conclusion, at the maintenance dose of 20 µg q.d., lixisenatide revealed no adverse ECG findings including in antibody-positive patients with T2DM (Study EFC6018).

Reviewer's comments: The sponsor conducted previously a TQT study TES6865. QT-IRT reviewed the study report and concluded that the study was inconclusive because assay sensitivity could not be demonstrated. No AEs of concern as per ICH E14 Guidance were reported.

No seizures, sudden deaths or ventricular arrhythmias were reported. No clinically relevant ECG changes were reported.

2.5 CLINICAL PHARMACOLOGY

Appendix 5.1 summarizes the key features of lixisenatide's clinical pharmacology.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report TES6865 for AVE0010, including electronic datasets and waveforms to the ECG warehouse.

3.2 TQT STUDY

3.2.1 Title

“Effect of repeated subcutaneous injections (20 µg once daily and 30 µg twice daily) of lixisenatide on ventricular repolarization, compared to placebo with moxifloxacin (400 mg single dose) as a positive control, in healthy subjects. A randomized, double-blind, double-dummy, 4-parallel group study.”

3.2.2 Protocol Number

TES11807

3.2.3 Study Dates

05 January 2011 -- 28 September 2011

3.2.4 Objectives

Primary objective:

“To assess the effect of a standard therapeutic and a supra-therapeutic dose regimen of lixisenatide administered as a repeated dose (14 days dose escalation + 14 days maintenance dose of 20 µg q.d. and 30 µg b.i.d.) on QTcF interval compared to placebo.

Secondary objectives:

- To assess the effect of lixisenatide on heart rate (HR), QT, QTcB, and QTcN, compared to placebo;
- To assess the clinical and laboratory safety of lixisenatide;
- To determine the plasma concentration of lixisenatide at the time of ECG investigation and assess the steady state pharmacokinetics of lixisenatide following repeated doses;
- To assess anti- lixisenatide antibody development after repeated dosing.”

3.2.5 Study Description

3.2.5.1 Design

This was a single center, randomized, double-blind, double-dummy, multiple dose, placebo-controlled study, and conducted in 4 parallel groups.

3.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

3.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were over encapsulated.

3.2.6 Treatment Regimen

3.2.6.1 Treatment Arms

The study was conducted in a 4-parallel group design and each subject received one of the 4 treatments as presented in following table:

Table 2: Treatment Groups

	Group 1	Group 2	Group 3	Group 4
lixisenatide	D1 to D7, 10 µg QD D8 to D14, 15 µg QD D15 to D28, 20 µg QD in the morning	D1 to D7 10 µg BID D8 to D14 20 µg BID D15 to D27 30 µg BID D28 30 µg in the morning		
lixisenatide placebo	D1 to D27 QD in the evening		D1 to D27 BID D28 QD in the morning	D1 to D27 BID D28 QD in the morning
moxifloxacin 400 mg				D28 QD morning
moxifloxacin placebo	D1 to D28 QD in the morning	D1 to D28 QD in the morning	D1 to D28 QD in the morning	D1 to D27 QD in the morning

QD – once daily; BID – twice daily; D – day

During the run-in phase, all subjects received lixisenatide placebo + moxifloxacin placebo in the morning only

Source: CSR Section 8.1 Table 1

3.2.6.2 Sponsor's Justification for Doses

A dose of 20 µg q.d. lixisenatide was shown to significantly lower HbA1c after 4 weeks of treatment. Therefore a dose of 20 µg q.d. is considered to already represent a therapeutically effective dose and may be potentially selected as the therapeutic standard dose. A dose of 30 µg b.i.d. is considered as a suprathreshold condition and is therefore selected for the second dose arm in this TES study. The dose regimen of 30 µg b.i.d. has been tested in two clinical studies (DRI6012, TES6865) and was found to be safe.

The two maintenance doses will be preceded by two different dose titration schemes. For 20 µg q.d., the preceding doses are 10 µg q.d. in the first week and 15 µg q.d. in the second week. For 30 µg b.i.d., the preceding doses are 10 µg b.i.d. in the first week and 20 µg b.i.d. in the second week. Therefore, it is assumed that the observations made in this study will cover future therapeutic and supra-therapeutic exposures.

*Reviewer's Comments: The selection of 20-µg q.d. as the therapeutic dose appears to be reasonable. The 30 µg b.i.d. represents the largest dose tested and is chosen as the suprathreshold dose. The overall exposure as well as the variability of the pharmacokinetic parameters increased largely in the antibody-positive subjects. The pharmacokinetic data in this study covered a wide range of lixisenatide exposure with mean values of C_{max} up to 209 pg/mL and AUC_{last} up to 979 pg*h/mL in antibody-*

negative subjects, and C_{max} up to 945 pg/mL and AUClast up to 12500 pg*h/mL in antibody-positive subjects.

Whether or not supratherapeutic dose is adequate will depend on the exposure increase in severe renal impairment. Lixisenatide exposure are significantly increased in patients with severe renal impairment. Nevertheless, the increase in lixisenatide exposure (e.g., C_{max}) was not reported (Highlights of Clinical Pharmacology).

3.2.6.3 Instructions with Regard to Meals

Lixisenatide or lixisenatide placebo was administered as a subcutaneous periumbilical injection 15 minutes prior to breakfast at approximately 8:00 AM and 15 minutes prior to dinner at about 6:00 PM from Day 1 to Day 27, in addition to a morning dose on Day 28 and the Day -1 run-in.

Reviewer's Comment: Acceptable. Since lixisenatide is administered as subcutaneous injection, food effects are not anticipated.

3.2.6.4 ECG and PK Assessments

"The assessment of ventricular repolarization was performed using 24-hour continuous 12-lead ECG recordings (Holter) on Day -1/Day 1 and Day 28/Day 29. Triplicate 10-second recordings were extracted from the Holter monitor at prespecified timepoints ranging from 30 minutes prior to investigational product administration to 24 hours afterward (T0.5H, T1H, T1.5H, T2H, T3H, T4H, T5H, T6H, T8H, T10H, T12H, and T24H).

"Plasma samples were collected at baseline (Day 1 predose); at T0.5H, T1H, T1.5H, T2H, T3H, T4H, T5H, T6H, T8H, T10H, T12H, and T24H on Day 28 postdose, and for assessment of Ctrough in the morning predose on Days 8, 15, 22, and 26 to 28."

Reviewer's Comment: ECG/PK sampling schedule appears to be reasonable.

3.2.6.5 Baseline

Time-matched Day-1 ECG measures were used as baseline.

3.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs was obtained while subjects are recumbent.

The assessment of ventricular repolarization was done using a 12-lead ECG (Marquette 5500) after at least 10 minutes in the supine position, before pharmacokinetic sampling.

Each ECG consisted of a 10 second recording of the 12 leads simultaneously, leading to:

- a single 12-lead ECG (25 mm/s, 10 mm/mV) printout for immediate safety and quality evaluation (HR, PR, QRS, QT, QTc automatic correction) including date, time, initials, and number of subject, signature of the Research Physician, and at least 3 complexes for each lead;

- a duplicated digital storage, which enabled manual reading (centralized reading of computerized ECGs), where applicable: each digital file was to be identified by

theoretical time (day and time PxxDxxTxxHxx), real date and real time (recorder time), sanofi-aventis study code, and subject number (eg, 3 digits) and initials (eg, 3 digits).

A computer-assisted, manual, on-screen measurement of digital ECG waveforms was secondarily performed using a standardized methodology.

ECG of each subject was presented to the reader in random order with no sequence identification information.

3.2.8 Sponsor's Results

3.2.8.1 Study Subjects

All 91 subjects randomized to the study were evaluated for safety. Since the prematurely discontinued 4 subjects had neither ECG nor plasma concentration measurements on Day 28, they have been excluded from pharmacodynamic and pharmacokinetic analysis. Three out of the 4 dropouts were replaced.

A greater percentage of male subjects (58.2%) were enrolled in the study compared to female subjects (41.8%).

3.2.8.2 Statistical Analyses

3.2.8.2.1 Primary Analysis

“Statistical analysis of time-matched mean difference estimates between T0H30 and T12H on Day 28 can be found in following table.

“The LTMMMD estimate for QTcF between the lixisenatide groups and placebo on Day 28 was 4.60 ms for 20 µg lixisenatide q.d. (90% CI: 2.34; 6.87) and 5.48 ms for 30 µg lixisenatide b.i.d. (90% CI: 3.22; 7.75). For both lixisenatide dose groups, the upper bound of the 90% two-sided CI for the largest time-matched mean effect of the drug on the QTcF interval was lower than 10 ms (Table 9).

“For both dose groups, the LTMMMD was observed at T3H.”

Table 3: Largest time-matched mean difference (LTMMMD) estimates between T0H30 and T12H on Day 28 - pharmacodynamic population (Sponsor's Results)

Change from time-matched baseline ^a in ECG Parameters	Comparison	Largest time-matched mean difference estimate between T0h30 and T12h			
		Theoretical time	Estimate ^b	2-sided 90% CI	
QTcF (ms)	Lixisenatide 20 µg QD vs. Placebo	T3H	4.60	2.34	6.87
	Lixisenatide 30 µg BID vs. Placebo	T3H	5.48	3.22	7.75
Heart rate (bpm)	Lixisenatide 20 µg QD vs. Placebo	T4H	7.29	5.61	8.96
	Lixisenatide 30 µg BID vs. Placebo	T4H	8.63	6.95	10.30
QTcN (ms)	Lixisenatide 20 µg QD vs. Placebo	T3H	3.39	1.09	5.68
	Lixisenatide 30 µg BID vs. Placebo	T3H	4.08	1.79	6.38
QT interval (ms)	Lixisenatide 20 µg QD vs. Placebo	T1H30	1.00	-3.51	5.51
	Lixisenatide 30 µg BID vs. Placebo	T1H30	-1.29	-5.80	3.21
PR interval (ms)	Lixisenatide 20 µg QD vs. Placebo	T1H	3.69	0.70	6.67
	Lixisenatide 30 µg BID vs. Placebo	T1H	5.01	2.03	8.00

CI=confidence interval

Number of subjects in the PD population : N=61 under lixisenatide 20 µg QD, N=61 under lixisenatide 30 µg BID, N=60 under placebo; these numbers can vary from one timepoint to another

^a The time-matched baseline for one timepoint is the value corresponding to the same theoretical timepoint on Day -1

^b The estimate is the difference of least square means between lixisenatide and placebo groups

Source: CSR Section 10.1 Table 9

Reviewer's Comments: please see the reviewer's analysis in section 4.2.

3.2.8.2.2 Assay Sensitivity

“The experimental conditions of the study were sensitive enough to document the QTc interval prolongation effect of the positive control, moxifloxacin (400 mg, single dose): the estimate of the mean difference between moxifloxacin and placebo for the change from time-matched baseline in QTcF across T3H, T4H, and T5H was 10.61 ms with a lower boundary of the 90% CI of 8.66 ms.”

Table 4: Assay sensitivity: change in QTcF from time-matched baseline across T3H, T4H, and T5H on Day 28 – pharmacodynamic population (Sponsor’s Results)

Change from time-matched baseline ^a	Comparison	Mean ^b across T3H, T4H and T5H		Mean difference across T3H, T4H and T5H	
		Moxifloxacin	Placebo	Estimate ^c	2-sided 90% CI
QTcF (ms)	Moxifloxacin 400 mg vs. Placebo	12.11	1.51	10.61	8.66 12.55

CI=confidence interval

^a The time-matched baseline for one timepoint is the value corresponding to the same theoretical timepoint on Day 1

^b Least square mean

^c The estimate is the difference of least square means between moxifloxacin and placebo groups

Number of subjects in the pharmacodynamic population : N=62 under Moxifloxacin, N=60 under placebo; these numbers can vary from one timepoint to another

Reviewer’s Comments: Our time-matched analysis indicates that moxifloxacin-induced QTc effect is established from this study.

3.2.8.2.3 Categorical Analysis

“No subject had a QTcF or QTcN value of ≥ 480 ms or ≥ 500 ms. Prolonged QTcF/QTcN values (>450 ms in male and >470 ms in female) were observed for QTcF in 1 subject in the moxifloxacin group only. No subjects had a change from baseline prolongation of >60 ms for QTcF or QTcN.

“The number of subjects with a borderline QTcF or QTcN value (431 to 450 ms in male, 451 to 470 ms in female) or borderline increase from baseline (30 to 60 ms) was comparable between both lixisenatide dose groups and placebo but was higher for moxifloxacin.

“For QTcB no subject was found to have a prolonged interval ≥ 500 ms or a change from baseline of >60 ms. One subject each in the 30 μg lixisenatide group and moxifloxacin group had a QTcB value of ≥ 480 ms. In the lixisenatide and placebo dose groups, the number of subjects with a borderline increase in QTcB was highest for placebo (8 out of 61), whereas for borderline change from baseline more subjects were affected in the 30 μg lixisenatide dose group (11 out of 62) than placebo (6 out of 61; lixisenatide 20 μg : 7 out of 61). In the moxifloxacin group the number of subjects with borderline increase and borderline change from baseline was higher than in placebo group.

“No subject had a PCSA for heart rate. On Day 28/29, very few subjects had a heart rate value of >90 bpm.

“Two subjects in each treatment group had a PR interval ≥ 220 ms, and a QRS interval prolongation of ≥ 120 ms was observed only in 2 subjects undergoing placebo treatment. Very few subjects had a PR >200 ms on Days 28/29.”

3.2.8.2.4 Additional Analyses

Heart rate analysis

The same statistical model was used to evaluate the $\Delta\Delta\text{HR}$ for treatment groups. The largest mean change of HR from baseline comparing to placebo is 7.29 bpm for 20- μg

q.d. lixisenatide dose group, and 8.63 bpm for 30- μ g b.i.d. lixisenatide dose group both occurred at 4 hour. The 95% upper limits were 8.96 bpm and 10.30 bpm, respectively.

3.2.8.3 Safety Analysis

Of the 91 subjects randomized, 4 subjects discontinued the study: 2 subjects discontinued the study on Day 1 due to technical problems with the ECG device, and 2 subjects discontinued due to an AE (due to urticaria and pruritic rash, withdrawal on Day 14 and Day 22, respectively).

The most frequent TEAEs were nausea and vomiting, which occurred mainly in the AVE0010 dose groups. There was only one subject (20 μ g q.d. AVE0010) with a single episode of vomiting on Day 28 about 2 hours after dosing and lasting about 1 minute. Most of these gastrointestinal events were mild to moderate in intensity. The 2 AEs, urticaria (30 μ g b.i.d. AVE0010) and pruritic rash (20 μ g q.d. AVE0010), resulted in premature withdrawal of the two affected subjects (on Day 14 and Day 22); both subjects developed anti-AVE0010 antibodies. In addition, few incidences of headache was also reported in both AVE0010 and placebo groups.

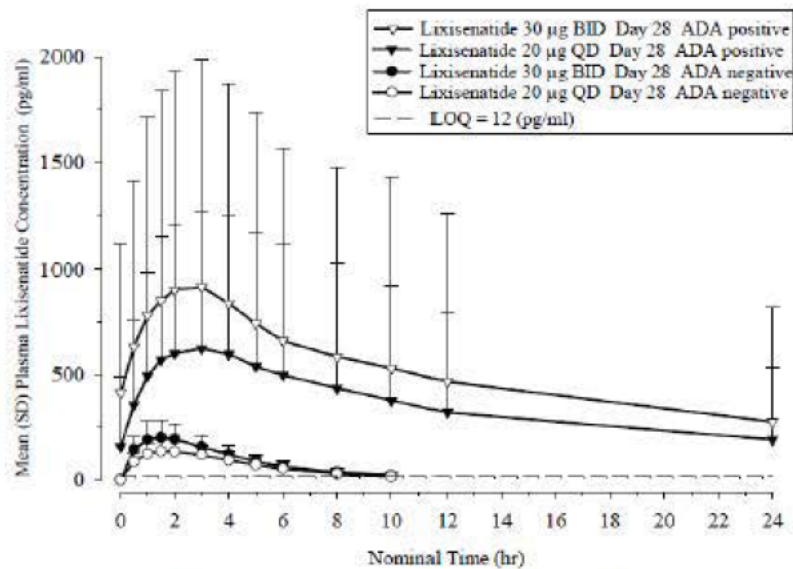
There were no SAEs reported in the study. There were no deaths reported in the study.

3.2.8.4 Clinical Pharmacology

3.2.8.4.1 Pharmacokinetic Analysis

Mean concentrations of lixisenatide by group and anti-drug antibody (ADA) status are shown in Figure 1. Mean PK parameters are shown Table 5.

Figure 1: Mean (+/-SD) Lixisenatide Plasma Concentrations at Day 28 by Group, and Antibody Status



Source = PK5 Study: TES11807, Scenario: P-D-A-EV-OD-E01, Version 1
 P-D-A-EV-OD-E01, Version 2

(Source: Sponsor's Study Report, Figure 14 on Page 131)

Table 5: Summary of Plasma Pharmacokinetic Parameters of Lixisenatide on Day 28, by Antibody Status

Mean ± SD (CV%) [Geometric Mean]	Lixisenatide plasma concentration Day 28			
	Lixisenatide 20 ug QD		Lixisenatide 30 ug BID	
	ADA negative	ADA positive	ADA negative	ADA positive
N	32	27	28	33
C _{max} (pg/mL)	144 ± 56.7 (39.4) [134]	662 ± 655 (98.9) [413]	209 ± 87.7 (41.9) [195]	945 ± 1080 (114.2) [575]
t _{max} ^a (h)	1.52 (1.00 - 5.02)	2.02 (1.00 - 6.00)	1.50 (0.50 - 3.00)	2.00 (0.50 - 5.02)
t _{1/2z} (h)	2.29 ± 0.515 (22.4) [2.24]	7.91 ± 6.44 (81.4) [5.63]	2.57 ± 0.452 (17.6) [2.53]	8.51 ± 7.01 (82.5) [6.34]
AUC _{last} (pg•h/mL)	705 ± 331 (47.0) [642]	8700 ± 11700 (134.5) [3330]	979 ± 346 (35.3) [922]	12500 ± 19100 (152.5) [4720]
AUC _t (pg•h/mL)	765 ± 357 (46.7) [700]	8710 ± 11700 (133.8) [3440]	960 ± 320 (33.4) [911]	7090 ± 9390 (132.3) [3520]

^aMedian (Min - Max)

(Source: Sponsor's Clinical Study Report, Table 26 on Page 133)

Reviewer's Comments: The sampling schedule appears adequate to characterize the steady state PK profile of lixisenatide. The overall exposure as well as the variability of the pharmacokinetic parameters increased largely in the antibody-positive subjects. The mean C_{max} and AUC of lixisenatide was approximately 40% higher at 30 µg b.i.d. than at 20 µg q.d. in antibody-negative subjects or antibody-positive subjects.

3.2.8.4.2 Exposure-Response Analysis

The sponsor performed PK/PD descriptive analyses including overlays, histogram, hysteresis, and scatter plots. Overlay plots show lixisenatide concentrations and delta delta or delta parameter (QTcF, HR, QTcN, QT, or PR) versus time. Histograms show distributions of time of maximum or minimum delta delta or delta parameter (QTcF, HR, QTcN, QT, or PR) overlaid with time of largest lixisenatide concentration. Hysteresis plots show delta delta or delta parameter (QTcF, HR, QTcN, QT, or PR) and lixisenatide concentrations. Scatter plots show delta delta or delta parameter (QTcF, HR, QTcN, QT, or PR) versus lixisenatide concentration and log of concentration. Plots are provided for all subjects in the PK/PD population and separately by anti-lixisenatide antibody status.

Reviewer's Comments: We conducted our own independent analysis. A plot of $\Delta\Delta QTcF$ vs. lixisenatide concentrations is presented in Figure 4.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcN (study-specific correction)) submitted by the sponsor. Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We also evaluated the linear relationships between different correction methods (QTcF, QTcN) and RR. The mixed model shows a smaller slope of QTcF vs. RR than that of QTcN vs. RR, which indicates that QTcF is a better correction method than QTcI for this study. We also looked at the Mean Sum of Squared Slopes (MSSS). The smaller this value is, the better the correction. Again, QTcF produces the smallest MSSS. Therefore, the FDA reviewer used QTcF for the primary statistical analysis. Sponsor also used QTcF as primary outcomes. We evaluated both QTcF and QTcN methods and found out that the results based on both methods are similar.

Table 6: Comparison of QTcF and QTcN Using the Mixed Model

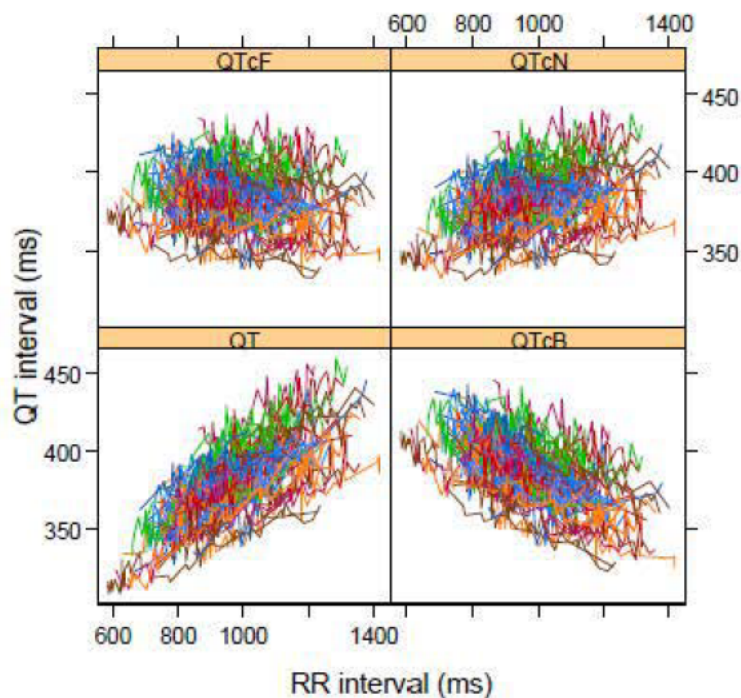
Treatment Groups	Slope of QTcF	Slope of QTcN	diff_p_value
All	0.01145	0.02780	<.001
Lixisenatide 20 ug q.d.	0.01013	0.02645	<.001
Lixisenatide 30 ug b.i.d.	0.01666	0.03330	<.001
Moxifloxacin	0.00972	0.02634	<.001
Placebo	0.00744	0.02339	<.001

Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	Treatment									
	Lixisenatide 20 ug q.d.		Lixisenatide 30 ug b.i.d.		Moxifloxacin		Placebo		All	
method	N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcF	61	0.0012	62	0.0014	63	0.0019	61	0.0012	247	0.0014
QTcN	61	0.0018	62	0.0022	63	0.0027	61	0.0017	247	0.0021

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, QTcF, and QTcN vs. RR (Each Subject's Data Points are Connected with a Line)



4.2 STATISTICAL ASSESSMENTS

4.2.1 QTc Analysis

4.2.1.1 The Primary Analysis for Lixisenatide

The statistical reviewer used mixed model to analyze the Δ QTcF effect using time-matched QTc at baseline day as baseline. The model includes sex as fixed effect and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

**Table 8: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group =
Lixisenatide 20 μ g q.d.**

Time/(hr)	Lixisenatide 20 μ g q.d.	Placebo	$\Delta\Delta$ QTcF	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-2.2	0.3	-2.4	(-5.5, 0.6)
1	-2.4	2.2	-4.6	(-7.9, -1.2)
1.5	1.1	1.3	-0.1	(-3.4, 3.2)
2	4.8	1.4	3.4	(0.2, 6.7)
3	5.4	0.7	4.6	(1.8, 7.5)
4	1.0	1.9	-1.0	(-4.0, 2.1)
5	-0.9	-0.4	-0.5	(-3.4, 2.5)
6	-0.9	0.6	-1.5	(-4.6, 1.6)
8	-2.7	2.7	-5.3	(-8.4, -2.2)
10	-3.1	-0.2	-2.8	(-6.1, 0.4)
12	0.1	0.2	-0.0	(-3.0, 3.0)
24	-0.1	0.2	-0.3	(-3.6, 3.1)

Table 9: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = Lixisenatide 30 μ g b.i.d.

Time/(hr)	Lixisenatide 30 μ g b.i.d.	Placebo	$\Delta\Delta$ QTcF	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-2.2	0.3	-2.5	(-5.5, 0.6)
1	-2.4	2.2	-4.6	(-7.9, -1.3)
1.5	2.1	1.3	0.8	(-2.5, 4.1)
2	4.4	1.4	3.1	(-0.2, 6.3)
3	6.2	0.7	5.5	(2.6, 8.3)
4	0.1	1.9	-1.9	(-4.9, 1.2)
5	-1.3	-0.4	-0.9	(-3.8, 2.0)
6	-1.5	0.6	-2.1	(-5.1, 1.0)
8	-5.1	2.7	-7.7	(-10.8, -4.6)
10	-4.9	-0.2	-4.6	(-7.8, -1.4)
12	-2.8	0.2	-3.0	(-6.0, -0.0)
24	-0.4	0.2	-0.6	(-3.9, 2.7)

The largest upper bounds of the 2-sided 90% CI for the mean difference between lixisenatide 20 μ g and placebo, and between lixisenatide 30 μ g and placebo were 7.5 ms and 8.3 ms, respectively, both occurred at 3 hours.

4.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model and time-matched baseline to analyze moxifloxacin and placebo data. The results are presented in Table 10. The largest unadjusted 90% lower confidence interval is 8.5 ms after considering Bonferroni multiple endpoint adjustment of three time points, which indicates that an at least 5 ms QTcF effect due to moxifloxacin was detected from the study.

Table 10: Analysis Results of ΔQ_{TcF} and $\Delta\Delta Q_{TcF}$ for Moxifloxacin 400 mg

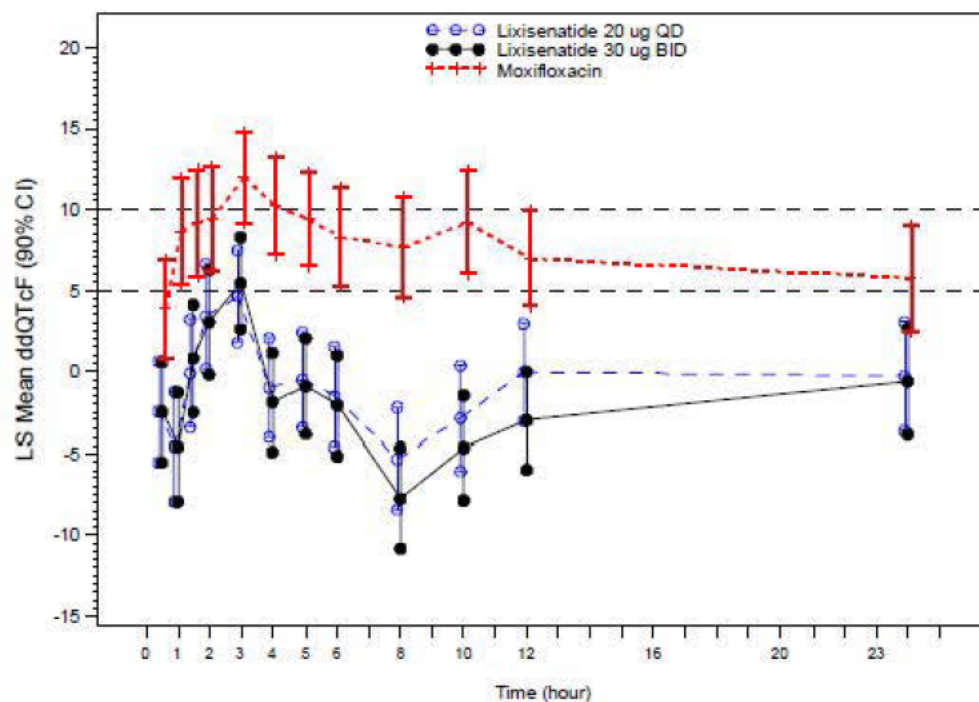
Time/(hr)	Moxifloxacin	Placebo	$\Delta\Delta Q_{TcF}^*$	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	4.2	0.3	3.9	(0.2, 7.6)
1	10.8	2.2	8.6	(4.6, 12.6)
1.5	10.4	1.3	9.2	(5.2, 13.2)
2	10.8	1.4	9.4	(5.5, 13.3)
3	12.7	0.7	12.0	(8.5, 15.4)
4	12.1	1.9	10.2	(6.5, 13.9)
5	8.9	-0.4	9.4	(5.8, 12.9)
6	8.9	0.6	8.3	(4.6, 12.0)
8	10.3	2.7	7.7	(3.9, 11.4)
10	9.0	-0.2	9.2	(5.3, 13.1)
12	7.1	0.2	7.0	(3.4, 10.6)
24	6.0	0.2	5.8	(1.8, 9.7)

- Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

4.2.1.3 Graph of $\Delta\Delta Q_{TcF}$ Over Time

The following figure displays the time profile of $\Delta\Delta Q_{TcF}$ for different treatment groups.

Figure 3: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

4.2.1.4 Categorical Analysis

In this study, no subject's QTcF was above 450 ms under any treatments.

Table 11: Categorical Analysis of QTcF

Treatment Group	Total N		Value<=450 ms		450 ms<Value<=480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	272	3253	269 (98.9%)	3238 (99.5%)	3 (1.1%)	15 (0.5%)
Lixisenatide 20 ug q.d.	61	730	60 (98.4%)	725 (99.3%)	1 (1.6%)	5 (0.7%)
Lixisenatide 30 ug b.i.d.	62	736	61 (98.4%)	730 (99.2%)	1 (1.6%)	6 (0.8%)
Moxifloxacin	63	755	59 (93.7%)	739 (97.9%)	4 (6.3%)	16 (2.1%)
Placebo	61	725	60 (98.4%)	716 (98.8%)	1 (1.6%)	9 (1.2%)

Table 12 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 12: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value<=30 ms		30 ms<Value<=60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Lixisenatide 20 ug q.d.	61	729	61 (100%)	729 (100%)	0 (0.0%)	0 (0.0%)
Lixisenatide 30 ug b.i.d.	62	736	60 (96.8%)	733 (99.6%)	2 (3.2%)	3 (0.4%)
Moxifloxacin	63	754	60 (95.2%)	750 (99.5%)	3 (4.8%)	4 (0.5%)
Placebo	61	725	60 (98.4%)	724 (99.9%)	1 (1.6%)	1 (0.1%)

4.2.2 HR Analysis

The same statistical analysis was performed based on heart rate using time-matched baseline. The point estimates and the 90% confidence intervals are presented in Table 13 and Table 14. The largest upper limits of 90% CI for the HR mean differences between lixisenatide 20 µg and placebo and lixisenatide 30 µg and placebo are 9.5 bpm and 10.7 bpm, respectively.

Table 13: Analysis Results of Δ HR and $\Delta\Delta$ HR for Lixisenatide 20 µg q.d.

Time/(hr)	Lixisenatide 20 µg q.d.	Placebo	$\Delta\Delta$ HR	
	Mean (bpm)	Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	-0.2	0.7	-0.9	(-3.2, 1.4)
1	-1.1	-0.2	-1.0	(-3.5, 1.6)
1.5	-0.5	-0.3	-0.2	(-2.6, 2.1)
2	0.5	-1.3	1.8	(-0.5, 4.0)
3	5.4	0.4	5.0	(2.6, 7.3)
4	7.6	0.2	7.3	(5.2, 9.5)
5	5.7	0.2	5.6	(3.1, 8.0)
6	5.5	1.3	4.2	(1.8, 6.7)
8	6.0	1.1	5.0	(2.7, 7.2)
10	3.4	1.7	1.8	(-0.4, 3.9)
12	2.3	-0.4	2.7	(0.4, 4.9)
24	3.1	3.2	-0.1	(-2.6, 2.4)

Table 14: Analysis Results of Δ HR and $\Delta\Delta$ HR for Lixisenatide 30 µg b.i.d.

Time/(hr)	Lixisenatide 30 µg b.i.d.	Placebo	$\Delta\Delta$ HR	
	Mean (bpm)	Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	1.1	0.7	0.5	(-1.8, 2.8)
1	-0.4	-0.2	-0.2	(-2.8, 2.3)
1.5	0.6	-0.3	0.9	(-1.4, 3.2)
2	1.2	-1.3	2.5	(0.2, 4.7)
3	6.1	0.4	5.7	(3.4, 8.0)

	Lixisenatide 30 µg b.i.d.	Placebo	ΔΔHR	
Time/(hr)	Mean (bpm)	Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
4	8.8	0.2	8.6	(6.5, 10.7)
5	7.7	0.2	7.5	(5.1, 9.9)
6	7.3	1.3	6.1	(3.6, 8.5)
8	7.9	1.1	6.9	(4.6, 9.1)
10	4.2	1.7	2.5	(0.4, 4.6)
12	4.0	-0.4	4.4	(2.1, 6.7)
24	3.0	3.2	-0.2	(-2.6, 2.3)

4.2.3 PR Analysis

The same statistical analysis was performed based on PR interval using time-matched baseline. The point estimates and the 90% confidence intervals are presented in Table 15 and Table 16. The largest upper limits of 90% CI for the PR mean differences between lixisenatide 20 µg and placebo and lixisenatide 30 µg and placebo are 7.3 ms and 8.7 ms, respectively.

Table 15: Analysis Results of Δ PR and $\Delta\Delta$ PR for Lixisenatide 20 μ g q.d.

Time/(hr)	Lixisenatide μ g q.d.	Placebo	$\Delta\Delta$ PR	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	5.3	5.1	0.2	(-3.1, 3.6)
1	6.3	2.7	3.6	(-0.1, 7.3)
1.5	5.1	3.6	1.4	(-2.2, 5.0)
2	3.9	4.4	-0.5	(-4.4, 3.3)
3	3.4	3.3	0.0	(-3.8, 3.8)
4	2.9	4.3	-1.3	(-4.8, 2.1)
5	1.5	3.0	-1.5	(-4.7, 1.7)
6	1.8	4.0	-2.2	(-5.4, 1.0)
8	0.8	3.5	-2.7	(-6.2, 0.8)
10	2.5	2.8	-0.3	(-3.7, 3.1)
12	-1.3	2.0	-3.3	(-6.3, -0.3)
24	3.3	5.6	-2.3	(-5.5, 1.0)

Table 16: Analysis Results of Δ PR and $\Delta\Delta$ PR for Lixisenatide 30 μ g b.i.d.

Time/(hr)	Lixisenatide 30 μ g b.i.d.	Placebo	$\Delta\Delta$ PR	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	7.1	5.1	2.0	(-1.3, 5.3)
1	7.6	2.7	5.0	(1.2, 8.7)
1.5	6.4	3.6	2.8	(-0.8, 6.4)
2	7.0	4.4	2.6	(-1.3, 6.4)
3	7.0	3.3	3.7	(-0.1, 7.4)
4	6.7	4.3	2.4	(-1.0, 5.9)
5	3.5	3.0	0.5	(-2.7, 3.7)
6	2.4	4.0	-1.5	(-4.7, 1.6)
8	4.0	3.5	0.5	(-2.9, 4.0)
10	4.8	2.8	2.0	(-1.4, 5.3)
12	1.4	2.0	-0.6	(-3.6, 2.3)
24	6.0	5.6	0.5	(-2.7, 3.7)

4.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 17 and Table 18. The largest upper limits of 90% CI for the QRS mean differences between lixisenatide 20 μ g and placebo and lixisenatide 30 μ g and placebo are 2.7 ms and 3.0 ms, respectively.

Table 17: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Lixisenatide 20 μ g q.d.

Time/(hr)	Lixisenatide 20 μ g q.d.	Placebo	$\Delta\Delta$ QRS	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	2.2	1.1	1.2	(-0.1, 2.4)
1	1.2	1.8	-0.6	(-2.0, 0.7)
1.5	0.6	1.5	-0.9	(-2.1, 0.3)
2	1.3	1.2	0.0	(-1.3, 1.4)
3	1.2	1.1	0.2	(-1.1, 1.4)
4	1.2	0.5	0.7	(-0.6, 2.0)
5	0.7	0.9	-0.1	(-1.5, 1.2)
6	1.2	0.9	0.3	(-1.0, 1.6)
8	0.0	-0.1	0.1	(-1.2, 1.4)
10	1.4	1.2	0.2	(-1.1, 1.5)
12	0.6	0.2	0.4	(-0.9, 1.6)
24	2.1	0.8	1.4	(0.0, 2.7)

Table 18: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Lixisenatide 30 μ g b.i.d.

Time/(hr)	Lixisenatide 30 μ g b.i.d.	Placebo	$\Delta\Delta$ QRS	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	1.7	1.1	0.7	(-0.6, 1.9)
1	1.4	1.8	-0.4	(-1.7, 0.9)
1.5	1.4	1.5	-0.1	(-1.3, 1.1)
2	1.4	1.2	0.2	(-1.1, 1.5)
3	1.2	1.1	0.1	(-1.2, 1.4)
4	1.1	0.5	0.6	(-0.7, 1.9)
5	1.4	0.9	0.6	(-0.7, 1.9)
6	1.3	0.9	0.4	(-0.9, 1.6)
8	0.0	-0.1	0.1	(-1.1, 1.4)
10	0.9	1.2	-0.3	(-1.6, 0.9)

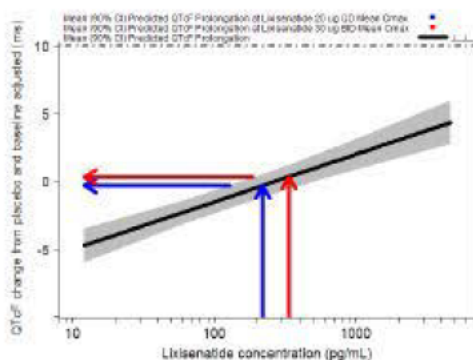
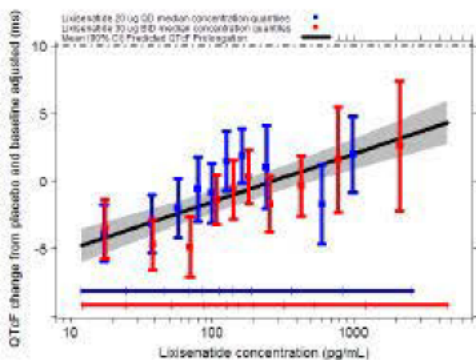
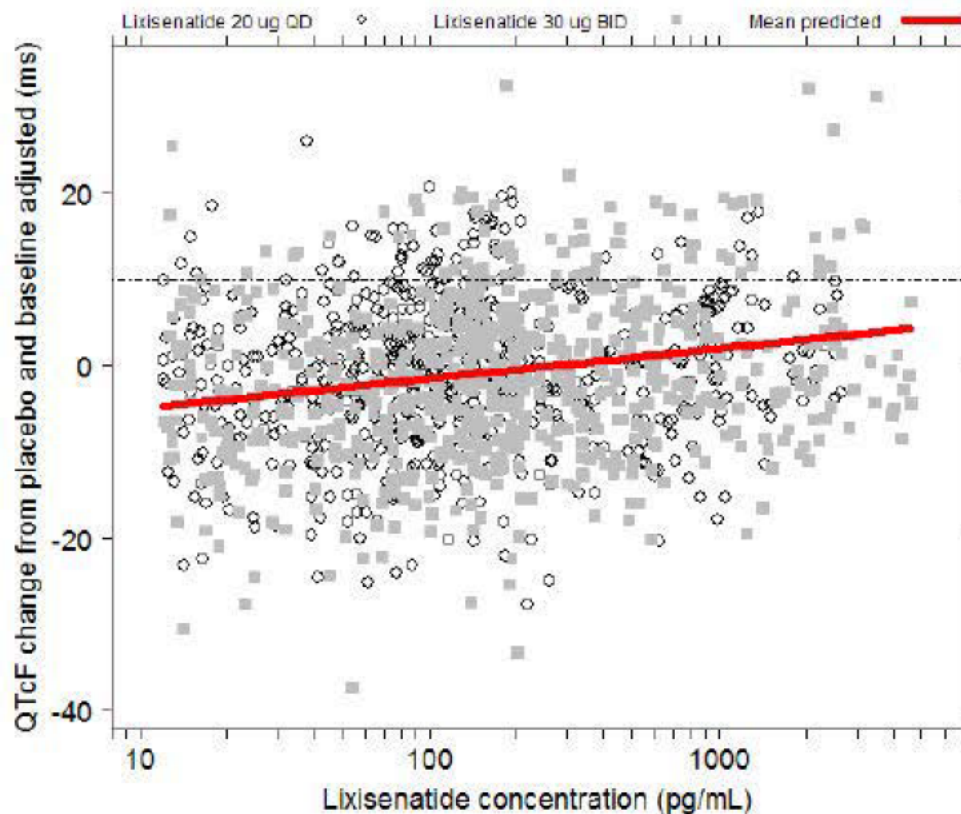
	Lixisenatide 30 µg b.i.d.	Placebo	ΔΔQRS	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
12	1.3	0.2	1.1	(-0.1, 2.4)
24	2.4	0.8	1.6	(0.3, 3.0)

4.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean lixisenatide concentration-time profile is illustrated in Figure 1. The overall exposure as well as the variability of the pharmacokinetic parameters increased largely in the antibody-positive subjects. The mean C_{max} and AUC of 30 ug b.i.d. dose was ~1.4-fold compared with lixisenatide 20 ug q.d. in the antibody-negative subjects or the antibody-positive subjects.

The relationship between $\Delta\Delta QTcF$ and lixisenatide concentrations is visualized in Figure 4. Based on visual diagnostics, the exposure-response relationship can be described better with a log-linear model compared to that with a linear model. As shown in Figure 4, the slope of $\Delta\Delta QTcF$ versus log lixisenatide concentration is positive and significant (slope 1.5266 with p-value <.0001 for a log-linear mixed effect model including intercept). However, there is no substantial QT prolongation in the exposure range at the therapeutic dose of 20 ug q.d. and the suprathreshold dose of 30 mg b.i.d. (Figure 4, bottom right panel). As stated earlier, it is not clear if 30 ug b.i.d. dose covers the high exposure clinical scenario (severe renal impairment).

Figure 4: $\Delta\Delta$ QTcF vs. Lixisenatide Concentration



4.4 CLINICAL ASSESSMENTS

4.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

4.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. According to ECG warehouse statistics less than 0.2% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

4.4.3 PR and QRS Interval

Overall 17 subjects had PR > 200 ms. However none of them had a PR > 218 ms. Post-baseline increases did not exceed 20% from baseline values.

There were 16 subjects who experienced QRS interval greater than 110 ms in drug treatment groups. No subject had a post baseline QRS > 118 ms or an increase over baseline > 10%.

5 APPENDIX

5.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	20 µg QD ¹	
Maximum tolerated dose	Single dose: 40 µg Multiple dose: Above 30 µg BID after dose titration ²	
Principal adverse events	Nausea, vomiting, abdominal pain, diarrhoea, flatulence, headache, asthenia and hypoglycemia (mostly in patients receiving concomitant sulfonylureas, not observed in healthy subjects). In a few cases allergic events including one anaphylactic reaction.	
Maximum dose tested	Single Dose	40 µg ³
	Multiple Dose	30 µg BID ⁴
Exposures achieved at Maximum tested Dose [Mean (CV%)]	Single Dose	10 µg ⁵ : - C _{max} = 60.3 (35%) pg/mL - AUC = 396 (31%) pg*h/mL
	Multiple Dose	30 µg BID ⁶ : - C _{max} = 184 (36%) pg/mL - AUC _{last} = 866 (34%) pg*h/mL
Range of linear PK	Linear PK was shown between 5-20 µg QD or BID.	
Accumulation at steady state	No accumulation in antibody negative subjects. In case of antibody formation, potential individual accumulation depending on properties of the multiclonal antibodies.	
Metabolites	No known active metabolites. Peptide drugs are normally degraded into smaller peptides and eventually to amino acids and renally cleared.	
Absorption	Absolute/Relative Bioavailability	No absolute BA study conducted. Rel. BA study testing site of SC injection with similar AUCs for abdomen, thigh and arm
	T _{max}	Median (range) for parent: 1.25 [0.75-2.25] h Median (range) for metabolites: not applicable
Distribution	V _z /F [Mean (CV%)]	242 (58%) L (at 20µg QD ⁶)
	% bound	The protein binding of lixisenatide was determined in vitro in human plasma by means of the ultracentrifugation method.

		Unbound levels of lixisenatide were quantified using an ELISA assay. Lixisenatide showed a moderate (55%) binding to human plasma proteins in the 500 to 50,000 pg/mL concentration range.
Elimination	Route	The expected consequence of medium-sized peptides is the degradation to small peptides and individual amino acids. Normally low molecular weight proteins as lixisenatide (~5000 Dalton) are filtered in the glomerulus, re-absorbed and proteolytically degraded in the renal tubulus.
	Terminal $t_{1/2}$	Mean (%CV) for parent: 3.62 (65.1%) h. Mean (%CV) for metabolites: not applicable.
	CL/F or CL	Mean (% CV): 25.75 (37.5%) L/h.
Intrinsic Factors	Age	So far no indication of age effect on PK.
	Sex	So far no indication of sex effect on PK.
	Race	In PDY6797 20-30 % difference in exposure level between Japanese vs. Caucasian, probably accounted to the body weight difference in the two ethnicities.
	Hepatic & Renal Impairment	No data available in hepatic impairment No relevant differences in C_{max} and AUC in patients with mild and moderate renal impairment. Significant increase in severe renal impairment.
Extrinsic Factors	Drug interactions	Lixisenatide has no inhibitory effect on drug metabolizing enzymes, interaction may occur due to delayed gastric emptying. For several compounds tested no effect on extent of absorption (AUC) if coadministered with lixisenatide was found. Due to the route of application (s.c.) an effect of other compounds on lixisenatide PK is unlikely.
	Food effects	Not applicable.
Expected High Clinical Exposure Scenario	30 µg lixisenatide BID, which is threefold the daily therapeutic dose of 20 µg QD, has been investigated in clinical studies DRI6012 (T2D patients), TES6865 and in TES11807 (thorough QTc studies with healthy subjects). 30µg BID is considered a supratherapeutic dose. Higher doses have not been tested but cases of overdose were	

	observed in the 13-week dose-ranging study DRI6012. Overdose did not result in specific adverse reactions, and sometimes were even asymptomatic. The exposure ratio for C_{max} and AUC between 20 µg OD and 30 µg BID was 2.1 and 2.6⁶. Cases of relative overdose may occur by non-compliance with the titration scheme, i.e. instead of a starting dose of 10 µg lixisenatide QD a patient injects 20 µg of lixisenatide QD. In this case the patient may experience gastrointestinal events, mostly nausea and less frequently vomiting.

- 1 route of injection was subcutaneous, refers to all doses mentioned in this table
- 2 multiple dose >30µg BID not tested
- 3 in T2D patients, FIM study AVE0010A/D1-016
- 4 in T2D patients for 8 weeks after prior up-titration, Phase IIIb study DR0012
- 5 single dose PK data from higher doses not available
- 6 from TES8865 in antibody negative healthy subjects after 4-weeks treatment incl. 2 weeks maintenance dosing with 30µg BID

5.2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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06/06/2012

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Reference ID: 3141052

4.3 OCP Filing Memo

Office of Clinical Pharmacology			
New Drug Application Filing and Review Form			
<i>General Information About the Submission</i>			
	Information		Information
NDA/BLA Number	204961	Brand Name	TBD
OCP Division (I, II, III, IV, V)	II	Generic Name	Lixisenatide
Medical Division	DMEP	Drug Class	GLP-1 receptor agonist
OCP Reviewer	Suryanarayana Sista, Ph.D.	Indication(s)	Treatment of Type 2 diabetes
OCP Team Leader	Lokesh Jain, Ph.D.	Dosage Form	Solution for subcutaneous injection
Pharmacometrics Reviewer	Ritesh Jain, Ph.D.	Dosing Regimen	10 µg as initiation dose and 20 µg as maintenance dose
Date of Submission	12/20/2012	Route of Administration	subcutaneous
Estimated Due Date of OCP Review	08/23/2012	Sponsor	Sanofi
Medical Division Due Date		Priority Classification	505 (b)(1) Standard
PDUFA Due Date	12/20/2013		

<i>Clinical Pharmacology and Biopharmaceutics Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	12		F2005KIN0016, F2005KIN0133, DOH0498, DME0135, DOH0499, F2005KIN0085, F2005KIN0148, AA43038, DOH0754, DOH1038, DOH1133, DOH1082
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:	X	2		F2005KIN0246, TRE0028
Blood/plasma ratio:				
Plasma protein binding:	X	1		LPR0930
Pharmacokinetics (e.g., Phase I)	X	2		TDU10121, 01-016
Healthy Volunteers-				
single dose:	X	9		BEQ11094, BDR6864, POP11814, POP6053, INT6052, INT6863, PDY11941, PDY11824, PDY11431

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
multiple dose:	X	8		POP11320, INT10408, INT10409, INT10782, INT10783, TES6865, TES11807, TDR11215
Patients-				
single dose:	X	3		01-016, PDY10433, PDY6797
multiple dose:	X	7		ACT6011, DRI6012, PDY6797, PDY10931, EFC6015, EFC6018, EFC10887
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1 ^a		POP11320 (dose proportionality assessed in Chinese subjects, this study is also listed under ethnicity studies)
Drug-drug interaction studies -				
<i>in-vivo</i> effects on primary drug:				
<i>in-vivo</i> effects of primary drug:	X	6 ^a		INT6052, INT6863, INT10408, INT10409, INT10782, INT10783
<i>in-vitro</i> :	X	3		MIH0797, MIH0544, MIH0332
Subpopulation studies -				
ethnicity:	X	2 ^a		POP11320, PDY6797
gender:				Pooled analysis of healthy subject data from Phase 1 studies performed
pediatrics:				
geriatrics:	X	1 ^a		POP11814
renal impairment:	X	1 ^a		POP6053
hepatic impairment:				
PD -				
Phase 1:	X	8 ^a		6 studies in healthy subjects (PDY11941, PDY11824, PDY11431, TES6865, TES11807, TDR11215); 2 studies in T2DM patients (01-016, PDY10433)
Phase 2:	X	4 ^a		ACT6011, DRI6012, PDY6797, PDY10931
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	6 ^a		PDY11431, PDY11941, PDY11824, TDR11215, TES6865, TES11807
Phase 3 clinical trial:	X	8 ^b		EFC6015, EFC6018, EFC10887, EFC10743, EFC11321, EFC6014, EFC6016, EFC6017
Population Analyses -				
Data rich:	X	7		POH0182, POH0268, POH0347, PMH0050, PMH0051, POH0343, POH0348
Data sparse:	X	2 ^a		EFC6014, EFC6018
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				

Clinical Pharmacology and Biopharmaceutics Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
solution as reference:				
alternate formulation as reference:	X	1 ^a		BDR6864 (Relative BA at 3 application sites)
Bioequivalence studies -				
traditional design; single / multi dose:	X	1 ^a		BEQ11094
replicate design; single / multi dose:				
Food-drug interaction studies				Not Applicable
Bio-waiver request based on BCS				Not Applicable
BCS class				Not Applicable
Dissolution study to evaluate alcohol induced dose-dumping				Not Applicable
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			Plan submitted, will be evaluated after review and approval of adult data
Literature References	X			
Total Number of Studies		59		

^aStudy/Studies already counted under [Healthy Volunteer Single-Dose](#) or [Healthy Volunteer Multiple-Dose](#) or [Patient Single-Dose](#) or [Patient Multiple-Dose](#)

^bEight (8) Phase 3 studies with PK data, 3 studies were already counted elsewhere

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Proposed commercial formulation is the same as the one used in Phase 1, 2 and 3 studies
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate			X	Partial waiver for age <10 years

	effectiveness, if the drug is indeed effective?				and deferral for ages 10-17 years sought
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comment to Sponsor:

In your Study POP6053 entitled “*Pharmacokinetics and safety of AVE0010 given as a single 5 µg subcutaneous dose in subjects with different degrees of renal impairment and in healthy subjects in an open, parallel group, non-randomized, single-dose study*”, you have used creatinine clearance range cut-offs based on the old guidance. Please reanalyze the renal impairment data based on the cut-offs indicated in the current guidance (dated 03/22/10, located at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf>).

Suryanarayana M. Sista 30 Jan, 2013

 Reviewing Clinical Pharmacologist Date

Lokesh Jain 30 Jan, 2013

 Team Leader/Supervisor Date

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

 Reviewing Clinical Pharmacologist Date

 Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURYANARAYANA M SISTA
04/08/2016

RITESH JAIN
04/08/2016

NITIN MEHROTRA
04/08/2016

MANOJ KHURANA
04/08/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208471	SDN	0000
Applicant	Sanofi-Aventis US LLC	Submission Date	27 Jul 2015
Generic Name	Lixisenatide	Brand Name	ADLYXIN
Drug Class	GLP-1 receptor agonist		
Indication	Treatment of Type 2 diabetes		
Dosage Regimen	• 10 µg as initiation dose and 20 µg as maintenance dose		
Dosage Form	Solution for subcutaneous injection	Route of Administration	subcutaneous
OCP Division	DCP 2	OND Division	DMEP
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Suryanarayana Sista, PhD	Manoj Khurana, PhD	
Pharmacometrics			
Genomics			
Review Classification	☒ Standard ☐ Priority ☐ Expedited		
Filing Date	9/10/2015	74-Day Letter Date	10/9/2015
Review Due Date	6/1/2016	PDUFA Goal Date	7/27/2016
Application Fileability			
Is the Clinical Pharmacology section of the application fileable?			
☒ Yes ☐ No If no list reason(s)			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?			
☐ Yes ☒ No If yes list comment(s)			
Is there a need for clinical trial(s) inspection?			
☐ Yes ☒ No If yes explain			
Clinical Pharmacology Package			
Tabular Listing of All Human Studies	☒ Yes ☐ No	Clinical Pharmacology Summary	☒ Yes ☐ No
Bioanalytical and Analytical Methods	☒ Yes ☐ No	Labeling	☒ Yes ☐ No
Clinical Pharmacology Studies			
Study Type	Count	Comment(s)	
In Vitro Studies			
☐ Metabolism Characterization			
☒ Transporter Characterization	1	TRE0028	
☐ Distribution			
☒ Drug-Drug Interaction	3	MIH0797 ^a , MIH0544 ^a , MIH0332 ^a	
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability	1	BDR12546	

☒ Relative Bioavailability	7	BDR6864 ^a (Relative BA at 3 application sites), BDR10880 ^b , BDR11038 ^b , BDR11540 ^b , BDR11578 ^b , BDR12547^b , PKD12406^b	
☒ Bioequivalence	1	BEQ11094 ^a	
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☒ Single Dose	9	BEQ11094 ^a , BDR6864 ^a , POP11814 ^a , POP6053 ^a , INT6052 ^a , INT6863 ^a , PDY11941 ^a , PDY11824 ^a , PDY11431 ^a
	☒ Multiple Dose	8	POP11320 ^a , INT10408 ^a , INT10409 ^a , INT10782 ^a , INT10783 ^a , TES6865 ^a , TES11807 ^a , TDR11215 ^a
Patients	☒ Single Dose	3	01-016 ^a , PDY10433 ^a , PDY6797 ^a
	☒ Multiple Dose	7	ACT6011 ^a , DRI6012 ^a , PDY6797 ^a , PDY10931 ^a , EFC6015 ^a , EFC6018 ^a , EFC10887 ^a
☐ Mass Balance Study			
☒ Other (e.g. dose proportionality)	2	POP11320 ^a (dose proportionality assessed in Chinese subjects, this study is also listed under ethnicity studies), TDU10121 (safety and PK of prolonged-release lixisenatide formulation)	
Intrinsic Factors			
☒ Race	2	POP11320 ^a , PDY6797 ^a	
☒ Sex		Pooled analysis of healthy subject data from Phase 1 studies performed	
☒ Geriatrics	1	POP11814 ^a	
☒ Pediatrics	1	PKD11475^c	
☐ Hepatic Impairment			
☒ Renal Impairment	1	POP6053 ^a	
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☒ Effects of Primary Drug	9	INT6052 ^a , INT6863 ^a , INT10408 ^a , INT10409 ^a , INT10782 ^a , INT10783 ^a , POH0398^d , POH0410^d , POH0384^d	
Pharmacodynamics			
☒ Healthy Subjects	7	PDY11941 ^a , PDY11824 ^a , PDY11431 ^a , TES6865 ^a , TES11807 ^a , TDR11215 ^a , PDY12545	
☒ Patients	8	01-016 ^a , PDY10433 ^a , ACT6011 ^a , DRI6012 ^a , PDY6797 ^a , PDY10931 ^a , PDY12625 , PKD11475^c	
Pharmacokinetics/Pharmacodynamics			
☒ Healthy Subjects	6	PDY11431 ^a , PDY11941 ^a , PDY11824 ^a , TDR11215 ^a , TES6865 ^a , TES11807 ^a	
☐ Patients	13	EFC6015 ^a , EFC6018 ^a , EFC10887 ^a , EFC10743 ^a , EFC11321 ^a , EFC6014 ^a , EFC6016 ^a , EFC6017 ^a , EFC12261 , EFC12626 , EFC11319 , EFC12703 , ACT12374	
☐ QT			
Pharmacometrics			
☒ Population Pharmacokinetics	9	POH0182 ^a , POH0268 ^a , POH0347 ^a , PMH0050 ^a , PMH0051 ^a , POH0343 ^a , POH0348 ^a , EFC6014 ^a , EFC6018 ^a	
☐ Exposure-Efficacy			
☐ Exposure-Safety			
Total Number of Studies	100		
Total Number of Studies to be Reviewed	13	In Vitro	In Vivo
		2	11

^aReviewed during first submission cycle as NDA 204961

^bLixisenatide and Insulin glargine (Lantus) combination studies

^cPediatric patients 10-17 years old, and adult patients

^dModeling and simulation studies of PK of oral acetaminophen (data from studies INT6863 and PDY12545)

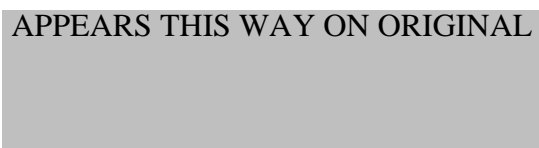
Bolded studies are new studies submitted in the current NDA 208471

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐ Yes ☒ No ☐ N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☒ Yes ☐ No ☐ N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☒ Yes ☐ No ☐ N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☒ Yes ☐ No ☐ N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☒ Yes ☐ No ☐ N/A	F2005KIN0016 ^a , F2005KIN0133 ^a , DOH0498 ^a , DME0135 ^a , DOH0499 ^a , F2005KIN0085 ^a , F2005KIN0148 ^a , AA43038 ^a , DOH0754 ^a , DOH1038 ^a , DOH1133 ^a , DOH1082 ^a , DOH1154 , F2005KIN0242
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☒ Yes ☐ No ☐ N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☒ Yes ☐ No ☐ N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☒ Yes ☐ No ☐ N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☒ Yes ☐ No ☐ N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was	☒ Yes ☐ No ☐ N/A	

previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☒ Yes ☐ No ☐ N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐ Yes ☐ No ☒ N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☒ Yes ☐ No ☐ N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☒ Yes ☐ No ☐ N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☒ Yes ☐ No ☐ N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐ Yes ☒ No ☐ N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐ Yes ☐ No ☒ N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☒ Yes ☐ No ☐ N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐ Yes ☐ No ☒ N/A	

Appendix

APPEARS THIS WAY ON ORIGINAL



NDA 20-8471 LIXISENATIDE INJECTION (AVE0010) [505 (b)(1)]

Sanofi

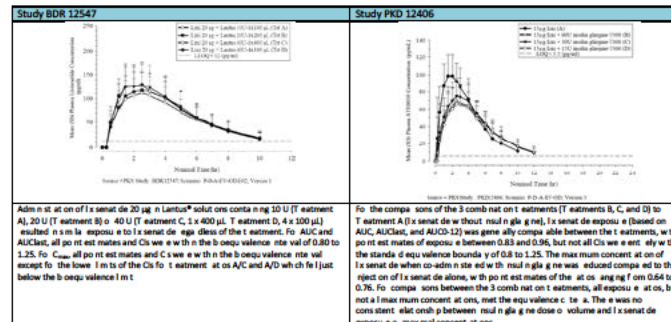
Clinical Pharmacology Review Team:

Sury Sista
Manoj Khurana (TL)

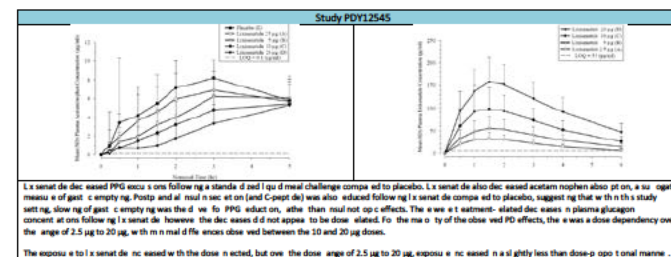
Overview: Clinical Pharmacology Program – Additional Information Since Original NDA

No.	Study	Objective
1	BDR12547	To assess the relative bioavailability, safety and tolerability of lixisenatide in the presence of Lantus U100 given in varying pharmaceutical forms
2	PKD12406	To assess the relative bioavailability, safety and tolerability of lixisenatide at 3 concentrations in insulin glargine U100 solution
3	DOH1154	Fourth generation assay: Double-antibody sandwich ELISA
4	DOH1082	ELISA assay for anti-lixisenatide antibodies
5	PDY12545	Dose-response relationship of different doses of lixisenatide on glucose profiles, gastric emptying, postprandial insulin, C-peptide and glucagon profiles, pharmacokinetics and safety
6	PKD11475	Assess the effect of lixisenatide on PPO, insulin, C-peptide, glucagon, safety, tolerability, pharmacokinetics and pharmacodynamics after a standardized liquid meal (breakfast) in pediatric and adult patients with type 2 diabetes
7	PDY12625	Investigate effects of repeated subcutaneous doses of lixisenatide 20 µg compared to Iraglutide 1.2 mg or 1.8 mg in reducing postprandial plasma glucose after a standardized solid breakfast; on postprandial plasma glucose excursion; plasma glucose; C-peptide; glucagon; HbA1c; body weight and waist circumference; heart rate and blood pressures; appetite perception; safety and tolerability.
8	POH0398 (data from INT6863)	Modeling and Simulation Study of Pharmacokinetics of Oral Acetaminophen
9	POH0410 (data from INT6863)	Modeling and Simulation Study of Pharmacokinetics of Oral Acetaminophen
10	POH0384 (data from PDY12545)	Modeling and Simulation Study of Pharmacokinetics of Oral Acetaminophen
11	EFC1261	Compare the efficacy and safety of lixisenatide injected prior to the main meal of the day versus lixisenatide injected prior to breakfast in type 2 diabetic patients not adequately controlled on metformin
12	EFC12626	Compare the efficacy and safety of lixisenatide to that of insulin glargine injected once-daily (OD) or thrice-daily (TD) in patients with type 2 diabetes not adequately controlled with insulin glargine alone or with metformin
13	EFC11319	To evaluate cardiovascular outcomes during treatment with lixisenatide, safety and tolerability
14	EFC12703	Effects of lixisenatide on glycemic control, safety, tolerability, pharmacokinetics, development of anti-lixisenatide antibody
15	ACT12374	Compare the efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination versus insulin glargine on top of metformin; pharmacokinetics of lixisenatide; development of anti-lixisenatide antibody

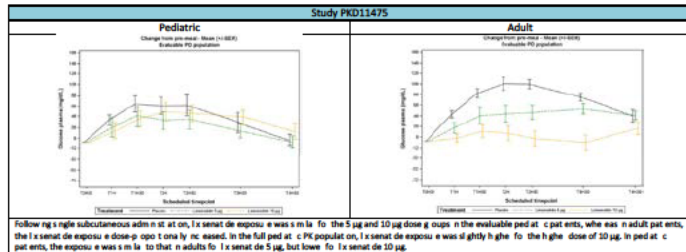
Results



Results

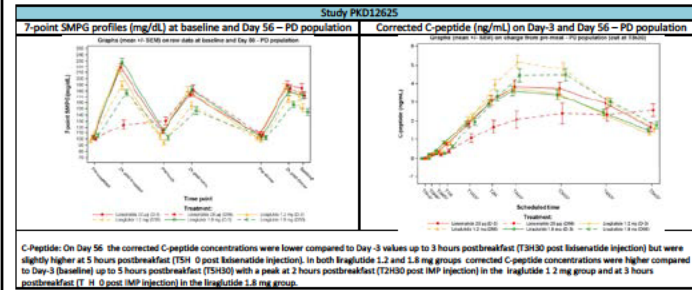


Results



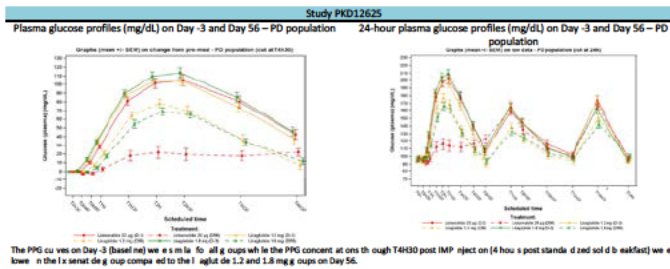
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Results



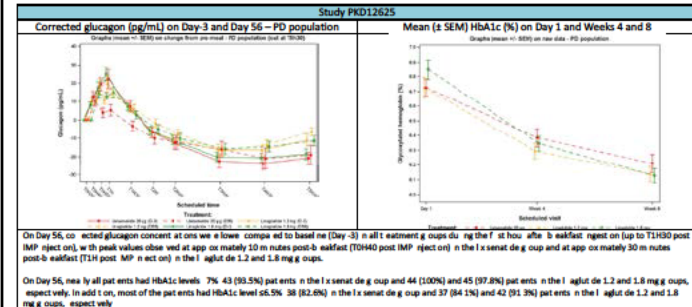
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Results

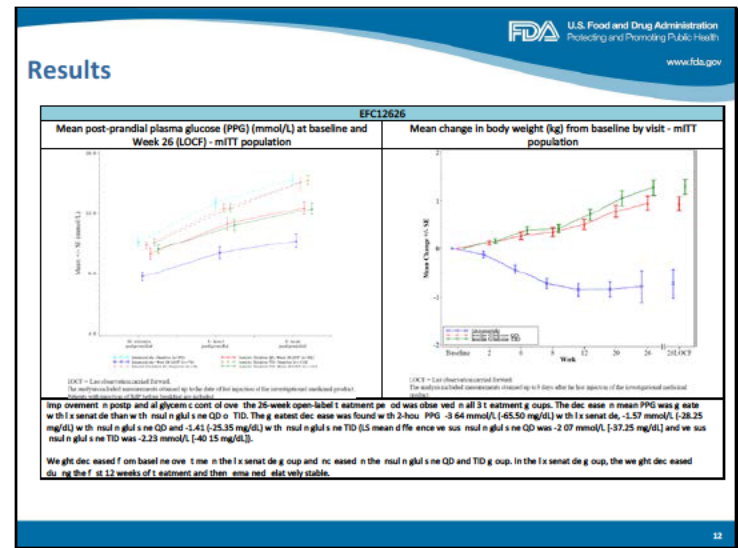
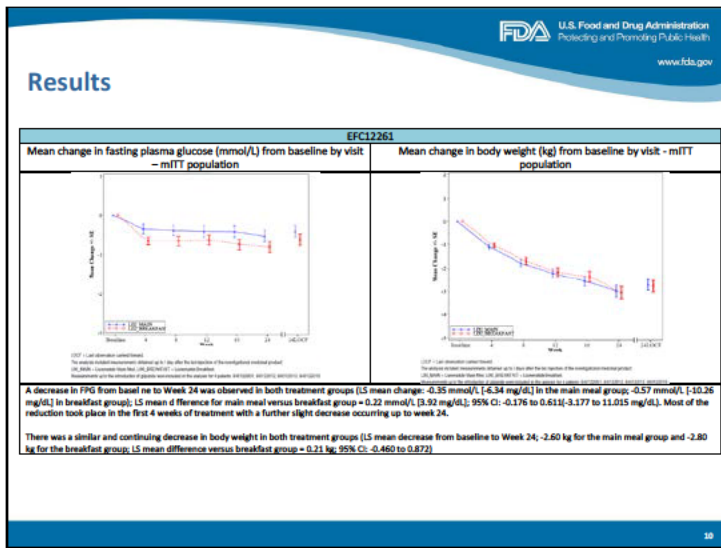
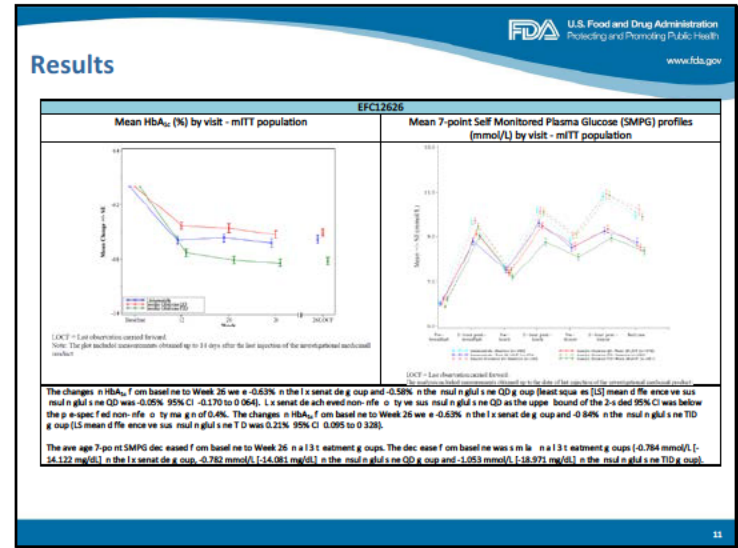
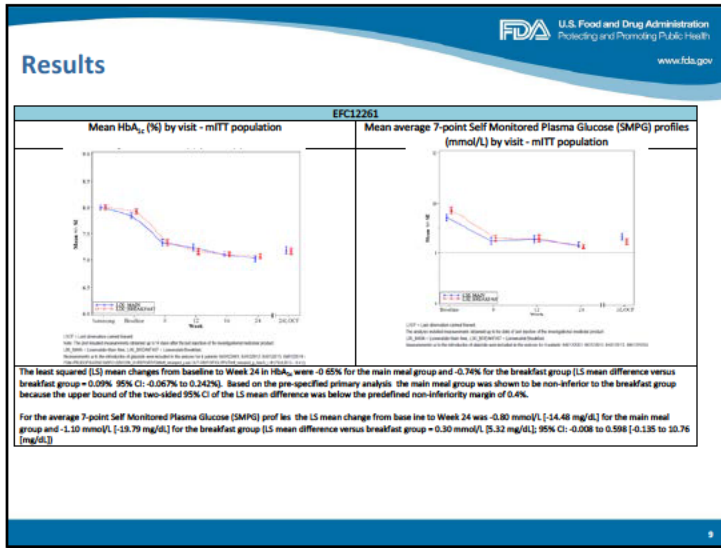


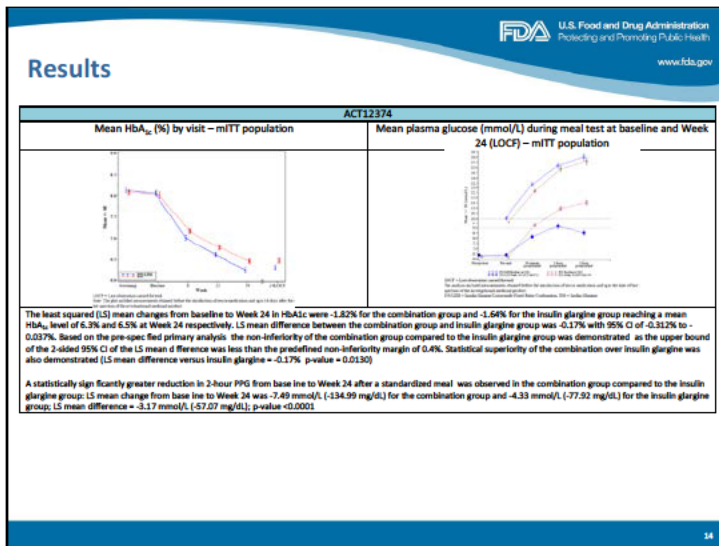
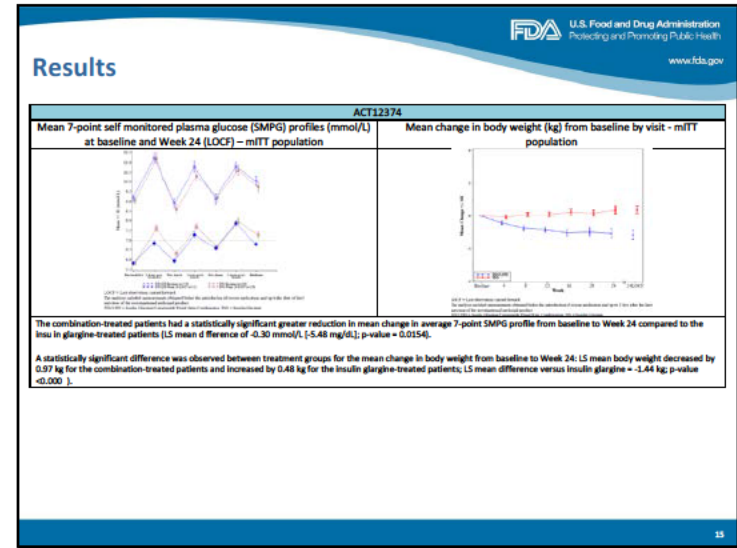
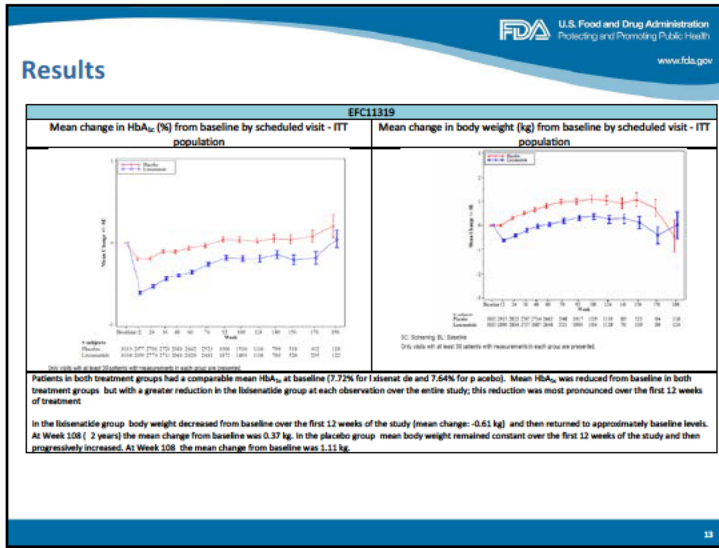
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Results



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Key Questions: Mid Cycle Deliverables

- Is there an update to the PK and PD features of lisinopril since the original NDA submission?
- Based on the additional information submitted, is there any need for dose adjustment based on intrinsic factors?
- Based on the additional information submitted, is there any need for dose adjustment based on extrinsic factors?

16

Conclusions

- This NDA is filable from OCP perspective
- No OSI inspection is requested

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURYANARAYANA M SISTA
11/12/2015

MANOJ KHURANA
11/12/2015