Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Lixisenatide

Proprietary Product Names: Lyxumia / Lyxumia Treatment initiation pack / Lixisenatide Sanofi / Lixisenatide Sanofi Treatment initiation pack / Lixisenatide Winthrop / Lixisenatide Winthrop Treatment initiation pack

Sponsor: Sanofi-Aventis Australia Pty Ltd

Date of CER: 5 December 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE:	Adverse Event
ANCOVA:	Analysis of Covariance
BMI:	Body Mass Index
CV:	Cardiovascular
CCV:	Cardiovascular and Cerebrovascular
CHF:	Congestive Heart Failure
CMI:	Consumer Medicine Information
CSR:	Clinical Study Report: this refers to Module 5 data submitted by the applicant
DSMB:	Data and Safety Monitoring Board
EU:	European Union
FDA:	Food and Drug Administration
FPG:	Fasting Plasma Glucose
GFR:	Glomerular Filtration Rate
GCP:	Good Clinical Practice
GI:	Gastrointestinal
HD:	High Dose
ITT:	Intent-To-Treat Population
IVRS:	Interactive Voice Recognition System
IM;	Internal Medicine
LD:	Low Dose
LFT:	Liver Function Test
LOCF:	Last Observation Carried Forward
LS:	Least Squares
K-M:	Kaplan-Meier

Abbreviation	Meaning
PD:	Pharmacodynamics
PI:	Product Information
Pk	Pharmacokinetics
PP:	Per Protocol
PRO:	Patient Reported Outcomes
PT:	Preferred Term
PTYs:	Patient Treatment Years
RAN:	Randomised Population
SAE:	Serious AEs
SAF:	Safety Population
SCS:	Summary of Clinical Safety
SD:	Standard Deviation
SOC:	System Organ Class
T2DM:	Type 2 Diabetes Mellitus
TEAEs:	Treatment Emergent AEs
TIA:	Transient Ischemic Attack
TZD:	Thiazolidinedione
SU:	Sulfonylurea
SYE:	Subject-Year Exposure
US:	United States

1. Introduction

1.1. Clinical rationale

Lixisenatide (AVE0010) is a GLP-1 receptor agonist. Type 2 Diabetes Mellitus (T2DM) is a progressive chronic illness characterised by hyperglycaemia due to defective insulin secretion and resistance to insulin action. Native GLP-1 is known to stimulate insulin release from the pancreatic islet cells, suppress glucagon secretion, delay gastric emptying, and reduce body weight (1). Although GLP-1 levels are reduced in patients with T2DM, their response to exogenous GLP-1 remains intact (2). The pancreatic effects are glucose dependent minimising the risk of clinically relevant hypoglycaemia (3). Non pancreatic effects of GLP-1 include slowing of gastric emptying, reduction of food intake, and an increase in satiety, all of which contribute to improving glucose control and decreasing body weight. The endogenous, active, circulating form GLP-1 (7-36)-amide has a very short half-life in circulation (90 to 120 seconds) mainly because of rapid N-terminal cleavage and inactivation by the dipeptidyl peptidase-4 (DPP-4) enzyme. The sponsor claims that lixisenatide is resistant to enzymatic cleavage by DPP-4. This results in a longer duration of action making it possible to use lixisenatide for therapeutic purposes. It was thus developed as a new treatment option to achieve glycaemic control in patients with T2DM.

1.2. Guidance

In the pre-submission data assessment form it is noted that the evaluator should refer to the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus CPMP/EWP/1080/00 which was adopted by the TGA in 2002. These Guidelines also refer to other guidelines i.e studies in support of special populations: geriatrics; dose response information to support drug registration; statistical principles for clinical trials; choice of the control group in clinical trials; fixed combination medicinal products; pharmacokinetic studies in man; and the note for guidance on the investigation of drug interactions.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

Modules 1 and 2 are in line with the TGA requirements for a category 1 submission.

In relation to Module 5, the following are submitted:

Clinical Pharmacology: 2 relative bioavailability studies; 4 relative bioavailability studies using admixture with insulin; 14 pharmacokinetic studies; 9 pharmacodynamic studies.

Efficacy: 10 efficacy and safety studies.

2.2. Good clinical practice

The sponsor states that the studies presented in this dossier have been undertaken in accordance with Good Clinical Practice (GCP), as required by the ICH E6 Guideline for Good Clinical Practice.

In 2 pivotal Phase 3 studies, 4 sites were terminated due to ongoing noncompliance with the clinical protocol and violations of GCP, in Study EFC 6016 and one of these sites was also involved in Study **EFC 6019**. One site (involving 5 subjects) was excluded based on a decision

prior to database lock; this was due to a serious noncompliance. Other sites were included in all analyses as they were stated to be "non serious". Details of these violations should be provided in the sponsor's response to this report.[1]

Comment: The scope of data provided in the clinical dossier is adequate for evaluation of this NCE. Relevant individual patient data are submitted. It is noted that the author of the clinical summary reports in Module 2 is an employee of Sanofi-Aventis.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

The table below lists the pk studies, and dose finding and efficacy studies with pk data. Pk data was also provided in PD and pk/PD studies.

Table 1: Submitted Pharmacokinetic Studies

Pk topic	Subtopic	Study ID
Pk in healthy adults	Bioequivalence different formulations - single dose	BEQ11094
	Bioavailability - obese otherwise healthy subjects	BDR6864
	Bioavailability – given mixed with Lantus	BDR11540
Pk in Special Populations	Renal impairment	POP6053
	Elderly	POP11814
	Healthy Chinese subjects	POP11320
Pk Interactions	Warfarin	INT10408
	Atorvastatin	INT10409
	Ramipril	INT10782

[1] The sponsor's response to the CER included the following clarification: In the 2 pivotal Phase 3 studies EFC6016 and EFC6019, research activities were terminated at 4 sites due to ongoing noncompliance with the clinical protocol and violations of GCP: sites due to ongoing noncompliance with the clinical protocol and violations of GCP: Site No. 630-625 (Puerto-Rico) in Study EFC6016 related to the management of patient safety. This site participated also in Study EFC6019 as Site No. 630--924 and was also closed in this study.; Site No. 840-608 (USA) in Study EFC6016 related to protocol adherence issues, Principal Investigator oversight, query resolution, and inappropriate source documentation practices; Site No. 840-910 (USA) in Study EFC6019 related to principal Investigator oversight, management of patient safety, and unavailability of patient clinic charts; Site No. 276-905 (Germany) in Study EFC6019 related to patients being allowed to continue taking antidiabetic medication, other than metformin, during study. Due to the seriousness of the noncompliance (intentional violation of inclusion criteria) at Site No. 276-905 (5 patients) in Study EFC6019, it was decided prior to database lock to exclude patient data from all efficacy and safety analyses in the clinical study report (CSR) and in the Clinical Summaries of Efficacy and Safety. Safety data of these patients were reported separately in the CSR. The patients from the other noncompliant sites were not excluded from the analyses because the noncompliance was considered to be non-intentional. Details are provided in the CSRs.

Pk topic	Subtopic	Study ID
	Digoxin	INT10783
	Paracetamol	INT6863
	Oral Contraceptive: ethnyloestradiol/levonorgestrel	INT6052
Population Pk analyses	Healthy subjects, special populations and target population	poh0182
	Target population	poh0215
		poh0216
Other		
Summary of Single dose pk in healthy subjects		
Summary of multiple dose pk in healthy subjects		
Pk data from a dose finding study in the target population		DRI6012
Pk data from efficacy studies in the target population		
Efficacy and safety as add on to sulfonylurea (with or without metformin).		EFC6015
Efficacy and safety as add on to basal insulin or basal insulin + metformin		EFC6016
Monotherapy		EFC6018
Efficacy and safety with 2 titration regimens as add on to metformin		EFC10743
Efficacy and safety in Asian patients insufficiently controlled with basal insulin with or without sulfonylurea		EFC10887
Safety and pk of 5 and 10µg lixisenatide single doses; efficacy, safety and pk of lixisenatide for 5 or 6 weeks, with dose escalation from 5 to 30µg in Japanese and Caucasian patients as add-on to sulfonylurea or sulfonylurea and metformin.		PDY6797

There were other pk studies submitted in this dossier that are not relevant to the formulation that applies to this application. Study **TDU10121** investigated a prolonged release formulation which was found to be unsuitable for further clinical development. This is not discussed further.

Bioavailability studies BDR 10880, BDR 11038, BDR 11540 and BDR 11578 were performed to compare fixed mixtures of lixisenatide and insulin with separate administration of each drug. The sponsor has not proposed admixture with insulin and thus, this is of limited relevance.

3.2. Summary of pharmacokinetics

3.2.1. Pharmacokinetics In Healthy Subjects and the Target Population

3.2.1.1. Absorption

Single dose healthy subject studies were BDR6864, BEQ11094, PDY11431, PDY11941, POP11814 and POP6053. Single dose studies in patients with T2DM included PDY10433 and PDY6797.

Single dose pharmacokinetic results in healthy adults: Different sites (abdomen, thigh and arm) have been used to inject SC lixisenatide. The dose range is 5 to 20 µg. These cross study comparisons did not show dose linear kinetics in relation to AUC and C_{max}. Median T_{max} in these studies ranged from 1.8 to 3.0 hours. Single dose studies in diabetic patients were obtained from PDY10433 and PDY 6796.The results on patients were generally similar and are included in the Table below.

Table 2: Single administration: Cmax and AUC healthy subjects and patients with T2DM (Ab-ve)

	AUC mean (%CV)		C_{max} mean (%CV)	
	Healthy Subjects	***Patients with T2DM***	***Healthy Subjects***	***Patients with T2DM***
5µg	258 (34)	175 (NC)	48 (52)	24 (31)
10µg	352 (37) - 410 (37)	365 (33)	49 (33) - 96 (36)	47 (56)
20µg	609 (30) - 970 (42)	503 (31)	97 (47)-171 (28)	82 (25)

Multiple dose studies in healthy subjects included in this submission are POP 11320, TES6865, INT10408, INT 10782 and 10783. The dose range used was 10 µg to 30 µg once daily for 7- 28 days. Study TES6865 also included a bd regimen. The geometric mean (CV) AUC 0-24h in these studies ranged from 547 (29) - 608 (68) pg.h/mL on day 14 to day 17 with 20 µg dose. In Study TES6865 a dose of 30 µg bd after 28 days resulted in AUC 0-24h of 808 (33) pg.h/mL . These were in antibody negative subjects.

Multiple dose studies on diabetic patients included ACT6011, DRI6012 and PDY6797. $AUC_{0\text{-}tau}$ refers to 0-24 hours and expressed as pg.h/mL; C max is pg/mL. The results as mean (CV) are as follows:

Table 3: Multiple administrations: Cmax and AUC patients with T2DM

	Patients with T2DM ($AUC_{(0\text{-}tau)}$)	*Patients with T2DM (Cmax)*
5µgQD	90 (4)- 241 (48)	28 (10)- 35 (32)
5µgBID	108 (25) - 491 (30)	35 (21)- 48 (34)

	Patients with T2DM ($AUC_{(0\text{-}tau)}$)	*Patients with T2DM (Cmax)*
10µgQD	175 (52) - 384 (42)	52 (49)- 76 (45)
10µgBID	175 (73) - 887 (27)	40 (56) - 106 (22)
20µg QD	298 (36) - 794 (40)	108 (39) - 175 (37)
20µgBID	517 (68) - 1658 (40)	90 (37)- 219 (39)
30µgQD	406 (37) - 447 (61)	84 (44) - 116 (37)
30µgBID	584 (24) - 840 (37)	144 (34) - 179 (10)

Presence of antibodies: In patients with T2DM who developed anti-lixisenatide Ab after multiple administrations, lixisenatide AUC and C_{max} were higher. This was associated with prolonged apparent terminal elimination half-life ($t_{1/2z}$) and increased median t_{max}. Findings from a multiple dose study, is given below where this is shown. This was a randomised placebo controlled study where lixisenatide 5 µg -20 µg was used qd or bd for 28 days. Steady state pk from this study is given below.

Table 4: Comparison of the mean values of selected AUC, Cmax, Tmax and half life data in the Ab-ve and Ab+ve groups

	Ab-ve		Ab+ve	
	QD (N=10)	**BID (N=8)**	**QD (N=10)**	**BID (N=8)**
$AUC_{[0:14h\text{-}23:55h]}$ (h*pg/mL)	847.76	1788.56	7250.7	40904.7
$AUC_{[0:14h\text{-}9:55h]}$ (h*pg/mL)	748.98	841.37	4395.8	16179.1
$Cmax_{[0:14h\text{-}23:55h]}$ (pg/mL)	187.20	234.38	703.63	2504.14
$Cmax_{[0:14h\text{-}9:55h]}$ (pg/mL)	187.20	216.05	696.33	2066.20
$tmax_{[0:14h\text{-}23:55h]}$ (h)	1.306	5.070	4.790	2.333
$tmax_{[0:14h\text{-}9:55h]}$ (h)	1.306	1.264	3.015	2.521
$t_{1/2\lambda z[0:14h\text{-}23:55h]}$	3.62	2.83	8.50	9.47
$t_{1/2\lambda z[0:14h\text{-}9:55h]}$	2.58	2.64	7.49	15.00

3.2.1.2. Bioavailability

The dossier does not include an absolute bioavailability study. However, there were two relative bioavailability studies, Study BEQ11094 and BDR 6864.

Study BEQ11094 was undertaken to determine the bioequivalence of 2 different formulations with different lixisenatide concentrations, 50µg/100mL (test [T]) and 100µg/mL (reference

[R]). These were the formulations proposed for marketing. Relative bioavailability of the T versus R formulation with 90% CI is shown below.

Table 5: CSR BEQ11094: Relative bioavailability analysis of lixisenatide test formulation versus lixisenatide reference formulation with 90% CI

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.

Study **BDR6864**: This was a randomised open label three way cross over study comparing the relative bioavailability of lixisenatide at 10 µg following subcutaneous injections at the abdomen, thigh and arm in obese otherwise healthy subjects. There was bioequivalence seen in relation to AUC; the C_{max} in relation to thigh vs abdomen did not meet the predefined criteria as seen below. The lack of an absolute bioavailability study also means that the reason for this inequivalence is not explained.

Table 6: CSR BDR6864: Relative bioavailability analysis of lixisenatide: thigh vs abdomen

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)
AUClast (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)

Justification for not providing an absolute bioavailability study was provided. Key points in the justification are: Nature of the dosage form- that it was intended for subcutaneous injection; it was stated to be highly soluble and without pH dependency; the pk is also not dose dependent; there is no first pass metabolism and there was comparative bioavailability with different strengths. The sponsor also states that the there is a margin between minimum effective dose and minimum toxic dose. The sponsor also states that all of these factors ie that its pharmacokinetic profiling and the clinical efficacy and safety studies would mean that the lack of absolute bioavailability is of limited significance.

Evaluator's comments: The evaluator does not agree with this justification. Without an absolute bioavailability study, it is not possible to fully characterise the pharmacokinetics of lixisenatide. The extent of absorption from each of the sites is not known; there is lack of equivalence in relation to C_{max} of thigh vs abdomen and this cannot be explained. This product is recommended to be administered once daily, it is not known whether it has any characteristics of a modified release presentation. It is also not known whether the formulation is optimally formulated.

3.2.1.3. Distribution

The approximate volume of distribution after single dosing of lixisenatide is as follows:

- Healthy subjects: 60 - 120 L Based on BDR6864, BEQ11094, PDY11431, PDY11941, POP11814, POP6053, INT10408, INT10409, INT10782, INT10783, POP11320 and TES6865.
- Patients with T2DM: 90 - 140 L Based on PDY10433 and PDY6797.

After multiple dosing the approximate volume of distribution was:

- Healthy subjects: 90 - 200 L Based on INT10408, INT10409, INT10782, INT10783, POP11320 and TES6865.
- Ab-ve patients with T2DM: 90 - 120 L Based on ACT6011, DRI6012 and PDY6797.

3.2.1.4. Metabolism

Lixisenatide is a peptide consisting of 44 amino acids, and therefore subject to standard proteolytic processes that result in degradation to small peptides and amino acids. Peptides (mean molecular weight <50 kDa) are assumed to be eliminated through renal filtration followed by tubular reabsorption and subsequent metabolic degradation.

3.2.1.5. Excretion

Lixisenatide is eliminated from plasma in healthy subjects and patients with T2DM with mean $t_{1/2z}$ generally ranging from 1.7 - 4.1 hours after single dose administration. In healthy subjects, this is shown in studies BDR6864, BEQ11094, PDY11431, PDY11941, POP11814 and POP6053. For subjects with T2DM, this is shown in studies PDY10433 and PDY6797.

After multiple dose administration lixisenatide is eliminated from plasma in healthy subjects and Ab-ve patients with T2DM with mean t1/2z from 1.4 - 4.5 hours. In healthy subjects, this is shown in studies INT10408, INT10409, INT10782, INT10783, POP11320 and TES6865. In Ab-ve patients with T2DM, this is shown in studies ACT6011, DRI6012 and PDY6797.

At steady state, the mean apparent total body clearance (CL/F) of lixisenatide ranged from 31-64 L/h in healthy subjects and from 20 - 67 L/h in patients with T2DM, with no consistent trends across dose levels. Also, clearance was decreased and apparent terminal half life was increased with Ab+ve status (study CSR ACT6011).

Lixisenatide is cleared primarily via metabolism in the kidney, in a study investigating the effect of renal impairment on the lixisenatide pk (POP6053), increases in the degree of renal impairment were accompanied by decreases in the mean CL/F of lixisenatide and corresponding increases in the exposure to lixisenatide (AUC) and $t_{1/2z}$.

Similarly, in a study on the effect of age on the lixisenatide pk (POP11814), the mean AUC parameters for lixisenatide in elderly subjects were approximately 1.3-fold higher than in younger subjects. As elderly subjects generally had lower CL_{CR} rates than younger subjects, part of the increased exposure to lixisenatide in the elderly subjects may be accounted for by their decreased renal clearance of lixisenatide.

No study is submitted that compares directly the pk of single dose and multiple dose administration. Thus there are no data on whether there is significant accumulation of lixisenatide with repeat dose administration.

3.2.1.6. Population pk analysis:

A population PK (Poppk) analysis (poh0182: data from studies BDR6864, POP6053, PDY6797 and DRI6012) indicated that lixisenatide has absorption-limited pk because the population mean absorption time (MAT) of 2.7 hours was longer than the population mean elimination time (V/CL) of 1.15 hours. Because of this, it is considered that measured rates of lixisenatide elimination can be considered as apparent rate of elimination.

3.2.2. Pharmacokinetics in Special Populations

3.2.2.1. Impaired Hepatic Function

No pk study was performed in subjects with acute or chronic hepatic impairment, and advanced hepatic impairment was an exclusion criterion in the clinical studies.

3.2.2.2. Impaired Renal Function

Study POP6053 assessed the pk and safety of lixisenatide in subjects with different degrees of renal impairment following a single 5µg dose. It was a single-centre, open-label, non-randomised, controlled, 4 parallel group study in 32 male or female subjects (aged 18 to 75 years, body weight >50 kg, and a body mass index (BMI) 18.5 - 35 kg/m^2 with normal renal function or with mild, moderate, or severe renal impairment (8 subjects per group).

Renal function categories based on creatinine clearance (CLCR) were > 80 mL/min = normal; 50-80 mL/min = mild impairment; 30 - < 50 mL/min = moderate impairment; < 30 mL/min (not requiring haemodialysis and not on dialysis from 2 weeks prior to enrolment visit to the end of study) = severe impairment.

The results showed that exposure (C_{max} and AUC) and CL/F were similar in subjects with normal renal function and those with mild renal impairment. With increasing degrees of renal impairment, however, exposure increased and clearance decreased. In subjects with severe renal impairment, the ratio estimate for AUC_{last} compared to subjects with normal renal function was 1.67; the 90% CI was (1.12 to 2.51). The ratio estimate for Cmax was 1.29 (90% CI: 0.90 to 1.86). The sponsor has included in the PI a precautionary statement that in those with renal clearance less than 30mL/min, Lyxumia should is not recommended. This statement is clearly inadequate and lixisenatide should be contraindicated in those with renal clearance < than 30mL/min. The findings of this study should be included in the PI.

3.2.2.3. According to age

Study POP11814 assessed the pk and safety of a single SC 20µg lixisenatide dose in healthy elderly male and female subjects and matched healthy young subjects. It was a single-centre, open-label, non-randomised study in 18 elderly (≥ 65 years) and 18 young (18 - 45 years) subjects matched for body weight and gender.

The results showed that AUC and AUC_{last} were higher in healthy elderly than in healthy young subjects, with treatment ratio estimates of 1.29 (90% CI: 1.06 to 1.57) and 1.26 (90% CI: 1.03 to 1.55), respectively. C_{max} and t_{max} were comparable in both study populations. For $t_{1/2z}$, the treatment ratio estimate was 1.57 (90% CI: 1.41 to 1.75).

These study findings should be included in the PI. The proposed statement, that age has no clinical effect of the pk of lixisenatide is not accurate and should be changed.

3.2.2.4. Ethnicity

Two studies examined this.

Study PDY6797 examined the pk of 5 and 10µg lixisenatide single doses and administration for 5 or 6 weeks, either once or twice daily following dose escalation from 5 to 30µg in 63 Japanese and 57 Caucasian T2DM patients, not adequately controlled with sulfonylurea or sulfonylurea and metformin. Treatment was up titrated to 30µg QD or BID from starting doses of 5µg 10µg QD or BID or volume matched placebo. In Ab-ve patients, the pk analysis showed that the mean AUC of lixisenatide was comparable across dose levels between Japanese and Caucasian patients with QD and BID dosing. The variability of the pk findings were high the findings of this study is of limited relevance.

Study POP11320 was undertaken to assess the pk of lixisenatide after repeated QD doses of 10 and 20µg in healthy young Chinese subjects (n=22). Lixisenatide 10µg QD was administered on days 1 to 7 with 20µg QD on days 8 to 14. Key pk parameters of lixisenatide after administration of multiple doses of 10 and 20µg in healthy young Chinese subjects were consistent with those observed in Caucasians. However, there was no study that directly compared the different ethnic groups.

In the Poppk study, poh0182, race was found to be a covariate (in addition to body weight) for the pk variability. However this effect was small and not considered to be clinically relevant. In

poh0215 and poh0216 body weight rather than (Asian/Japanese) race was found to be a confounding factor among the covariates tested for their effect on the exposure to lixisenatide.

3.2.3. Pharmacokinetic Interactions

3.2.3.1. Pharmacokinetic Interactions Demonstrated In Human Studies

These studies were conducted on healthy adult volunteers.

Warfarin: INT10408: This was a Phase I single centre study of 16 healthy males where 25 mg of warfarin and lixisenatide (10 µg for 7 days and 20 µg for 7 days) were administered. There were no significant changes to the pk of either drug. Based on the results of this study, there is a recommendation in the PI that dose adjustment is not necessary. This is acceptable from the evaluator's point of view.

Atorvastatin: INT10409: Here morning and evening administration of atorvastatin (40 mg) was investigated with co-administration of lixisenatide (10 µg for 7 days followed by 20 µg for 7 days) in 36 healthy male volunteers.The pk of lixisenatide was not assessed. When administered in the evening, atorvastatin C_{max} increased (together with lixisenatide) – 14.0 (ng/mL) ± 9.15 vs 7.50 (ng/mL) ± 4.40, when administered alone. AUC was not affected. No dosing changes are recommended in the PI and this is accepted by the evaluator.

Ramipril: INT10782: This study (n=30) administered 5 mg ramipril with or without lixisenatide. (The dose of lixisenatide was 10 µg for 7 days followed by 20 µg for 7 days). There was no effect of 20µg QD lixisenatide on the rate or extent of ramiprilat (the active metabolite of ramipril) on absorption in healthy subjects. For the prodrug ramipril, the 90% CI of the ratio estimates for AUC_{τ} was (point estimate of 1.21; 90% CI: 1.06 to 1.39). C_{max} was decreased: the 90% CI (point estimate of 0.37; 90% CI: 0.29 to 0.46). These findings are included in the draft PI. This study did not assess the effect of ramipril on lixisenatide.

Digoxin: INT10783: The dosing schedule for digoxin was 0.25 mg digoxin bd for one day and followed by 0.25 mg/ day for 6 days. The dose of lixisenatide was similar to previous studies. Whilst most pk parameters did not show a significant change, the C_{max} of digoxin (when administered with lixisenatide reduced from 1.52 ng/mL ± 0.466 to 1.18 ng/mL ±0.465. T_{max} also increased from 0.52 to 2.00 hours. This is consistent with the known effect of lixisenatide on gastric emptying. These findings are included in the draft PI.

Paracetamol: INT6863: This study used 1000 mg paracetamol and 10 µg lixisenatide in 15 subjects. C_{max}, t_{max}, AUC_{last}, and AUC of paracetamol were not affected when paracetamol was administered 1 hour before 10µg lixisenatide. When paracetamol was administered 1 or 4 hours after lixisenatide, t_{max} of paracetamol increased to a median of 4.50 hours (from 0.5 hours), and C_{max} of paracetamol was decreased by 29% and 31%, respectively, as compared to placebo control. AUC_{last} and AUC remained unchanged. These effects reflect the delaying effect of lixisenatide on the gastric emptying rate. This poses a problem if paracetamol is administered for pain management and administered 1-4 hours after lixisenatide administration. Optimum effect may not be achieved. The findings of the study are included in the draft PI.

Oral Contraceptive: INT6052: Ethinyloestradiol 0.03 mg/levonorgestrel 0.15 mg: In healthy post-menopausal female subjects, lixisenatide 10µg had no effect on the pk of a single dose of oral contraceptive when injected 11 hours before and/or 1 hour after intake of the oral contraceptive. When lixisenatide was injected 1 or 4 hours before administration of the oral contraceptive, t_{lag} and t_{max} of ethinyloestradiol and levonorgestrel were increased, C_{max} of ethinyloestradiol was decreased by 52% and 39%, respectively, and C_{max} of levonorgestrel was decreased by 46% and 20%, respectively. AUC_{last}, AUC, and $t_{1/2z}$ of ethinyloestradiol and levonorgestrel were unchanged. Based on the results of this study, there is a statement in the draft PI that the Cmax is of 'limited clinical significance' and there is no need to adjust the dose of OC when co-administered with lixisenatide. It is recommended that the statement, limited clinical significance be removed as this cannot be assumed based on a single dose pk study.

3.2.4. Pharmacokinetics and Antibody Status

An overview of the anti-lixisenatide Ab assays used in the clinical studies is shown in the table below.

Table 7: Anti-lixisenatide antibody assays in clinical studies

	F2005KIN0085-amend02 (F2006KIN0192, AA21755) Radioimmunoprecipitation method	DOH0754 (EN-E01) Biacore method
Single dose studies in healthy subjects	BDR6864, INT6052, INT6863, POP6053	BEQ11094
Single dose studies in patients with T2DM	PDY6797	-
Multiple dose studies in healthy subjects	TES6865	INT10408, INT10409, INT10782, INT10783, POP11320
Multiple dose studies in patients with T2DM	ACT6011, DRI6012, PDY6797	EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10780, EFC10781, EFC10887, EFC11321, LTS10888

The number of healthy subjects or T2DM patients with anti-lixisenatide Ab in the pk population is presented below. These data are consistent with those presented in the respective CSRs, either in the body of the report or appendices.

The number of Ab+ve subjects is only those in the pk population and include all who had a positive result before or during the study and were Ab+ve on the day of pk profiling.

Table 8: Numbers of healthy subjects or T2DM patients with anti lixisenatide Ab in the pk population

	Number of healthy subjects or patients with T2DM			
	Treated with lixisenatide	Lixisenatide PK population		
Study		**All**	**Antibody-negative**	**Antibody-positive [a]**
Single dose studies - healthy subjects				
BDR6864	43	43	42	1[b]
BEQ11094	90	90	89	1[b]
POP6053	32	32	32	0
Single dose studies - patients with T2DM				
PDY6797	80	40	39	1[b]
Multiple dose studies - healthy subjects				
INT10408	16	16	9	7
INT10409	34	34	18	16
INT10782	30	29	15	14
INT10783	24	24	15	9
POP11320	22	21	14	7
TES6865	47	43	30	13
Multiple dose studies - patients with T2DM				
ACT6011	42	42	23	19
DRI6012	433	127	54	73
PDY6797	80	78	56	22

In the **healthy subject studies**:

- The 2 healthy subjects in single dose studies were +ve at baseline.
- In the 6 multiple dose studies in healthy subjects, 45/128 (26.9%) who were Ab-ve at baseline developed Ab, with most observed for the 1st time within 3 weeks of treatment.
- The longest treatment duration of multiple dose lixisenatide administered to healthy subjects was 28 days in study TES6865. In this study, approximately 30% of subjects

developed Ab. With 20µg QD, lixisenatide AUC was substantially higher in Ab+ve subjects with approximately a 7-fold increase for mean AUC parameters and 3.3-fold for mean Cmax compared to Ab-ve subjects. Also, the median tmax was delayed by 1.5 hours in Ab+ve subjects and the mean t1/2z increased by 4.7 hours. The inter-individual variability of the pk parameters increased markedly in Ab+ve subjects.

- The remaining 4 studies with multiple dose pk data in healthy subjects, INT40408, INT40409, INT10782, and INT10783 were all drug-drug interaction studies with shorter durations of lixisenatide treatment (up to 17 days). In these, 46/103 (45%) subjects developed Ab. Ab status had no relevant effects on the mean concentrations of lixisenatide.

T2DM studies:

- In the three phase 2 studies in patients with T2DM, 98/198 (39.7%) subjects who were Ab-ve at baseline developed Ab; in most these were observed for the 1st time within 5 weeks of treatment (54/ 98 subjects) or after 6 - 13 weeks (36/98 subjects).
- In study DRI6012, in which patients with T2DM were treated with lixisenatide at doses of 5, 10, 20, or 30µg QD or BID for up to 13 weeks, Ab were measured at weeks 4 and 13; across treatment groups, the incidence of Ab positivity at week 4 (QD dosing: 13.5% to 30.9%; BID dosing: 22.2% to 44.2%) was less than at week 13 (QD dosing: 39.2% to 56.4%; BID dosing: 60.4% to 64.8%); at both time points the incidence was generally lower with QD than BID dosing; at the last measurement, there was no consistent relationship between incidence of Ab and lixisenatide dose level with either QD or BID dosing.
- In studies with patients with T2DM the following is noted. In Study ACT6011, increased lixisenatide concentrations in Ab+ve patients were only apparent at the highest dose levels, 20µg QD and BID, which also involved the longest treatment durations. The increase in mean AUC in Ab+ve patients compared to Ab-ve patients was 5.6-fold with 20µg QD and 7.7-fold with 20µg BID. The increases in Cmax were not so large, 3.2-fold with 20µg QD and 4.8-fold with 20µg BID, and were accompanied by delays in median tmax. The mean CL/F was decreased in Ab+ve patients, and there was a corresponding increase in the mean t1/2z. The interindividual variability of the pk parameters generally increased markedly in the Ab+ve subjects in these treatment groups.

4. Pharmacodynamics

The table below lists the PD, PD/pk and Poppk/PD studies.

Table 9: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on glucagon and other counter regulatory hormones during hypoglycaemia in healthy subjects	PDY11941
	Effect on the first and second phase insulin response, second-phase C-peptide secretion responses and glucose disappearance rate, and on glucagon release in subjects with T2DM	PDY10433
	Effects of treatment with lixisenatide or liraglutide on the postprandial plasma glucose in patients with type 2 diabetes not adequately controlled with metformin.	PDY10931

PD Topic	Subtopic	Study ID
Secondary Pharmacology	Effect on gallbladder motility in healthy male and female subjects.	PDY11431
	Effect on sperm production in healthy subjects	TDR11215
	Effect on ventricular repolarisation in healthy subjects	TES6865
Population PD and pk-PD analyses	First in man; healthy subjects safety, tolerability, and maximum tolerated dose (MTD), single dose pk, effect on oral glucose tolerance, plasma insulin, unesterified free fatty acid, C-peptide, and glucagon levels	01016
	PD, safety, tolerability and pk in patients with type 2 diabetes mellitus	ACT6011
	Pk/PD analysis of lixisenatide in Diabetes Type II patients in study **PDY6797**	PMH0051
	Pk, PD safety and tolerability in patients with type 1 diabetes mellitus	BDR10880
		BDR11038
		BDR11578
	Pk/PD Analysis of lixisenatide in Diabetes Type II patients in study **DRI6012** and comparison to study **PDY6797**	PMH0050

Studies **BDR10880**, **BDR11038** and **BDR11578** are in patients with Type 1 DM and are therefore not relevant to this application as the proposed indication is for T2DM.

4.1. Summary of pharmacodynamics

This section presents information on pharmacodynamic parameters measured in Phase 1 and 2 studies. Information on the pharmacodynamic parameters that were efficacy variables in the dose finding and efficacy and safety studies are presented in the section on Clinical Efficacy of this report.

4.2. Primary pharmacodynamics

Stimulation of insulin secretion: This study **PDY10433** was a single dose (20 µg of lixisenatide) study that investigated the insulin response under euglycaemic clamp conditions in 22 subjects with T2DM. The first phase (0-10 min) mean (sd) insulin release with lixisenatide (n=20) vs placebo (n=20) was 2835.38 pmol.min/L (1778.15) vs 502.64 (384.78) pmol.min/L respectively. The second phase (10 min to 120 min) results are presented as point estimate and 90% Confidence Intervals. The AUC of insulin and C-peptide release for lixisenatide vs placebo were 2.96 (2.65-3.29) and 2.08 (1.88-2.31) respectively.

Study **01-016** was a phase I, double blind placebo controlled ascending single dose safety and tolerability study in T2DM patients (n=36) who were randomised in groups of 6 to receive 1.0, 3.0, 10, 20 and 40 µg of lixisenatide. The 60 µg dose was abandoned due to reduced tolerability.

A liquid carbohydrate meal was administered one hour after injection of lixisenatide or placebo. Plasma glucose, C peptide, plasma insulin, unesterified FFA and serum glucagon were measured. The increase in mean glucose in the 1 and 3 µg group was less pronounced than placebo. There was no increase in mean glucose observed with the 10 to 40 µg groups. Other pharmacodynamic endpoints reflected these trends (i.e no significant effect in placebo, 1-3 µg; the significant effect in the 10 to 40 µg group). 10 µg was deemed the maximum tolerated dose as there were no adverse events reported with this dose; 50% of all adverse events were reported with the 20 µg dose.

Similar trends were also observed in the placebo-controlled phase 2 studies ACT6011, PDY6797 and DRI6012.

PDY 10931. This is a multicentre open label parallel group study on 148 patients not controlled with ≥ 1.5 g metformin/ day comparing liraglutide with lixisenatide. Liraglutide was administered once daily for 28 days (0.6mg/day for 1-7 days, 1.2 mg/day on days 8-14, 1.8 mg on days 15- 28). Lixisenatide 10 µg (1-14 days) and 20 µg (15-28 days) were the doses used. The primary pharmacodynamic variable was the change from baseline to Day 28 in AUC plasma glucose concentration time curve from time of standardised breakfast start (30 minutes after injection of the drug) until 4 hours later. Lixisenatide produced a reduction of -227.25 h.mg/dL (95% CI; -246.88 to -207.61). The change observed with liraglutide (n=68) was -72.83 h.mg/dL (95% CI: -93.19 to -52.46). The change between these groups was statistically significant favouring lixisenatide. The change in post-prandial insulin was also significant favouring lixisenatide with the treatment difference if -69.56 µIU/mL ($p<0.0001$).

Suppression of glucagon secretion: In Study **PDY10433** reduction in mean glucagon concentrations were seen under the euglycaemic clamp conditions in 2 hours between a single dose of lixisenatide 20µg and administration of the IV glucose challenge. In contrast, the mean glucagon concentrations increased during this time period after administration of placebo. After the glucose challenge, lixisenatide did not affect glucagon release compared to placebo.

In **Study 01-016** the normalisation in blood glucose after an oral glucose load given 1 hour after a single dose of 10, 20, and 40µg lixisenatide was accompanied by small changes in mean glucagon concentrations.

In the placebo controlled Phase 2 studies **ACT6011** and **PDY6797** postprandial suppression of glucagon following administration of lixisenatide was seen.

Increase in insulin sensitivity: In study **ACT6011**[2], insulin sensitivity was evaluated in terms of beta cell function using the homeostasis model assessment (HOMA). The changes were similar in the lixisenatide and liraglutide groups. This was an exploratory analysis with limited significance.

Gastric emptying: This effect was investigated using the 13C-octanoic acid breath test in study **ACT6011** in patients with T2DM. There were increases in the mean half-life and lag-time after treatment with lixisenatide 10 and 20µg in the QD and BID groups (compared with placebo). Results show that there was an increase in half-life of > 2 hours with 20µg.

Also, in study **INT6863**, the median t_{max} for paracetamol increased from 0.25 to 4.5 hours when administered 1 hour after lixisenatide, and the mean C_{max} of lixisenatide decreased by approximately 30% when administered 1 hour before or 1 or 4 hours after paracetamol reflecting the delaying effect of lixisenatide on the gastric emptying rate.

Reduction in body weight: In study **ACT6011** mean weight reductions compared to placebo were not seen with lixisenatide with 10 or 20µg QD or BID dosing. Study **PDY10931** showed a reduction at 28 days in the lixisenatide group (1.6 kg) and liraglutide group (2.4 kg). This was a safety endpoint in the pharmacodynamic study. In study **PDY6797** which was a dose escalation

[2] Sponsor correction: 'Study ACT6011' should read 'Study PDY10931'.

study (5-30 µg) with QD and BID lixisenatide treatment for up to 6 weeks the mean reductions were approximately 0.42 and 0.67 kg in the lixisenatide groups

Satiety markers were assessed in Study **PDY10931** in investigation of the PD effects of lixisenatide 20µg QD compared to liraglutide 1.8 mg QD in patients with T2DM. There were no consistent trends observed; it is not posisble to interpret these results without correlation to an objective endpoint relating to weight loss in larger number of subjects.

Fasting blood glucose: The overall trend seen in the placebo-controlled Phase 2 studies, **ACT6011**, **PDY6797** and **DRI6012** was that, compared to placebo, multiple dose treatment with lixisenatide resulted in decreased fasting blood or plasma glucose concentrations across the dose level range of 5 to 30µg with QD and BID regimens, except 5µg BID in study **DRI6012**.

Study **ACT6011** was a dose titration Phase II study where lixisenatide 5, 7.5, 10,12.5, 15.0, 17.5 and 20 µg were administered in a total of 64 subjects with T2DM. There was a trend of dose response at the higher dose range, however the numbers were too small to be conclusive.

In study **PDY6797** the mean reductions in fasting plasma glucose (FPG) from baseline with lixisenatide compared to placebo were significant at the 20µg dose based upon data for the highest well tolerated dose, which was 20µg in most patients.

Longer term treatment results are provided in Study **DRI6012**. This is a Phase 2, double blind placebo controlled study of 13 weeks (n=542). Lixesenatide 5, 10, 20 or 30 µg bd doses were compared with 20 or 30 µg once daily. FPG was a secondary efficacy endpoint. There was a dose dependent decrease reaching a maximum effect at 30 µg. The effect appeared greater with the bd dose.

Postprandial blood or plasma glucose*:* Similar changes (to that of FPG) were also observed in these studies- **01016**, **ACT6011**, **PDY6797**, **DRI6012**. There was greater evidence of dose response at the higher doses examined i.e 10, 20 and 40 µg. There was no clinically significant difference between once and twice daily doses in the number examined.

In study **PDY10931**, when the PD effects of lixisenatide 20µg QD on day 28 of treatment were compared to liraglutide 1.8mg QD in patients with T2DM the mean change in plasma glucose was the primary pd endpoints. The mean change from baseline in postprandial glucagon $AUC_{0:30\text{-}4:30h}$ was -227.25 mg.h/dL with lixisenatide and -72.83 ng.h/mL with liraglutide. The estimated mean treatment difference was -154.42 ng.h/mL [95% CI: -180.3 to -128.54] for lixisenatide compared to liraglutide ($p < 0.0001$).

Other: Results for the following are consistent with and support the findings for FPG and PPG:

- Average 7-point blood glucose profile: study ACT6011
- Fructosamine: studies PDY6797 and DRI6012
- HbA1c: Study DRI6012, which was the placebo-controlled dose ranging study to determine the dose of lixisenatide for the Phase 3 program.

The effect of race on the PD effects of lixisenatide was investigated in Study **PDY6797** in a comparison of Japanese (n=63) and Caucasian (n=57) patients. This was a dose escalation study (5-30 mcg) where lixisenatide was administered once or twice daily. In relation to the primary efficacy endpoint (PPG) the mean difference vs placebo in the qd or bd groups in the Japanese cohort was -406.7 and -346.3 h*mg/dL and in the Caucasian cohort-260.1 and -231.3 h*mg/dL. This difference has been attributed to the difference in body weight 66 kg in the Japanese vs 86 kg in the Caucasian group. This has not been verified, however.

Effect of anti-lixisenatide antibodies on pharmacodynamics related to efficacy*:* In study **DRI6012**, after up to 13 weeks of treatment with lixisenatide, the incidence of anti lixisenatide Ab formation varied between 43.1% and 71.2% across lixisenatide doses of 10, 20, and 30µg with QD or BID. As the numbers were small in each of the dosing groups and those with the

presence of antibodies (ranging from 17 to 36), the results relating to HbA_{1C} had wide variability to make a meaningful conclusion. Clearly, results on antibodies need to be verified with larger Phase III studies.

4.3. Secondary Pharmacodynamic Effects

Pharmacodynamic response under hypoglycaemic conditions: Study **PDY11941** examined whether the counter-regulatory hormone response (glucagon, cortisol, adrenalin, noradrenalin, growth hormone) and hypoglycaemia awareness is preserved during provoked hypoglycaemia with lixisenatide. A hypoglycaemic clamp procedure was used to assess the effects of a single 20 µg dose of lixisenatide on the response during induced hypoglycaemia and the recovery of blood glucose levels on termination of the glucose clamp in 18 healthy volunteers. Results of this showed the lack of lixisenatide effect on glucagon response to hypoglycaemia under the conditions of the study.

Gallbladder motility: In the crossover study **PDY11431,** the single dose administration of 20µg lixisenatide significantly reduced the gall bladder ejection fraction (GBEF) in response to cholecystokinin (CCK-8) compared to placebo at 60 minutes by 45.8% (95% CI: 29.92% to 61.68%). This was a study on 20 healthy subjects. The findings of this study need to be confirmed in patients to be of relevance.[3]

Electrocardiogram parameters: Study **TES6865,** a placebo and active (moxifloxacin 400mg single dose) controlled study of lixisenatide 20 µg or 30 µg bd for 28 days to investigate the potential for delayed ventricular repolarisation in 91 healthy subjects. None of the changes in corrected QT intervals approached any of the thresholds of concern. It is noted that a second "thorough QT/QTc study (TES11807)" is being conducted. This is presumably to satisfy the requirement of the EU Guideline on QT/QTc prolongation (CHMP/ ICH/2/04) and is to be conducted in patients. The sponsor should state the progress of this study.[4]

Spermatogenesis: Study **TDR11215** was conducted in healthy subjects to assess the effects of lixisenatide (20µg/day for 6 months) compared to placebo on spermatogenesis. The primary outcome measure was the proportion of subjects (%) with at least 50% reduction in sperm concentration from baseline at the end of a 26-week treatment period. The point estimate was 3.81% in the placebo group and 8.93% in the lixisenatide group. Non-inferiority of lixisenatide compared to placebo was demonstrated, as the upper limit of the 95% CI for the mean difference in proportion of subjects with ≥ 50% reduction in sperm concentration for lixisenatide versus placebo was 12.439%, which is below the pre specified non-inferiority margin of 20% (p = 0.1452). This magnitude of the non-inferiority margin should be justified to ascertain the clinical relevance of this study.[5]

4.4. Time Course of Pharmacodynamic Effects

Using mixed effects modelling, the effect of lixisenatide on plasma glucose concentrations was investigated on 2 time scales: hours after a breakfast challenge for postprandial plasma glucose on several occasions and days for FPG on several occasions using a previously developed Poppk model.

In the population PD/pk study, **PMH0051**, results from study **PDY6797** were used to assess the time for effect of lixisenatide on FPG and on postprandial glucose after the breakfast challenge. It was found that the time scale for effect on FPG is several days. However, the effect on postprandial glucose after a breakfast challenge is much faster being about 1 hour. The

[3] Additional information on this issue was provided in the sponsor's response to the CER (not presented here).
[4] The sponsor's response to the CER stated: "The Study TES11807 has now been completed and the CSR is available upon request."
[5] Justification was included in the sponsor's response to the CER (details not presented here).

maximum effect of lixisenatide on the glucose AUC after a standard breakfast in study **PDY6797** is a reduction of 20.5 mmol/L*h (95% CI: 17.3 to 23.7) for the population mean. The lixisenatide AUC_{50}, where half of the effect was observed, is approximately 162 pg/mL*h (95% CI: 88 to 236).

Data from study **DRI6012** were used for study **PMH0050** and were less informative than data from study **PDY6797**. Trends for FPG were similar to those for study **PDY6797**. However, there was not enough data to use for PopPD/pk analysis of the breakfast challenge for study **DR16012**.

4.5. Relationship between Drug Concentration and Pharmacodynamic Effects

In Study ACT**6011** in patients with T2DM, the relationship between change in blood glucose AUC[0:14h-4:55h] and lixisenatide AUC[0:14h-9:55h] at the 5, 10, and 20µg doses was investigated graphically in patients (QD: N=9, BID: N=11), who were Ab-ve at day 29. There were no clear signs of a relationship between AUC for lixisenatide and the change in blood glucose AUC at any of these dose levels. Data for the 20µg dose is also presented in the submission. In a comparison of the 20µg QD and BID regimens, there was no difference for lixisenatide AUC and for blood glucose AUC between these treatment groups. In this, the increased exposure to lixisenatide with BID dosing did not translate into an increased PD effect. Similar trends were seen with the 5 and 10µg doses.

4.6. Evaluator's overall conclusions

4.6.1. Pharmacokinetics:

There are 11 pk studies submitted. These were conducted in 367 healthy volunteers. There were two relative bioavailability studies; there were also 5 drug interaction studies.

The two dose strengths proposed for marketing (50 µg/mL and 100 µg/mL) have been shown to be bioequivalent using the accepted criteria for bioequivalence, i.e 90% CI of 80 -120%. These formulations are identical to the formulations used in the clinical trials.

Study **BDR 6864** which examined the relative bioavailability of three sites (thigh, abdomen and arm) did not show bioequivalence in relation to C_{max} relating to thigh vs abdomen. It is not possible to assess whether this is clinically significant as there is no absolute bioavailability study submitted. Thus, the pk of this product has not been fully characterised. Whether this formulation is optimally developed is not known. Similarly, it is not known whether there is any modified release characteristics in this product or there is any degradation at the site of the injection.

The lack of absolute bioavailability and the lack of bioequivalence in relation to C_{max} in the relative bioavailability study should be included in the PI.

The single dose pharmacokinetic studies in healthy and diseased subjects did not reveal a clear dose linear kinetics. Multiple dose studies also reflected similar findings; twice daily regimen had increased AUC compared with once daily regimen.

The terminal half life after multiple dose administration in healthy and diseased subjects ranged from 1 to 4 hours. The total body clearance in those with T2DM was 20-67 L/h.

Lixisenatide is cleared renally. One study POP6053 studies the effect of the pk of lixisenatide (5 µg) after a single dose in those (n=32) with varying degrees of renal impairment. Whilst those with mild renal impairment did not show any significant effect, the other categories of renal impairment showed increased exposure and decreased clearance. As this is a single dose study, it does not provide information on multiple dosing. The proposed PI only includes a precautionary statement that lixisenatide should not be used in those with Cr Cl less than 30 mL/min. Unless the sponsor provides multiple dose studies showing it does not affect the pk

significantly, lixisenatide should be contraindicated in those with any degree of renal impairment.

One single dose study on the elderly (POP11814) using 20 µg lixisenatide showed an increase in AUC in comparison to younger subjects. AUC ratio of elderly/ young: 1.29 (CI 1.06 to 1.57). The effect of multiple dosing is not known. This should be included in the PI; the statement that age had "no clinically relevant effect on pk based on population pk data" analysis should be removed as the weight of evidence of the above mentioned study contradicts this finding.

The studies on different ethnic backgrounds have been studied in Japanese, Chinese and Caucasian backgrounds. As these are studies with varying results, no conclusion can be drawn on the effect of lixisenatide on race. The statement in the PI that there were 'no clinically relevant effects' based on these studies should be qualified, as these studies that showed wide variability and of limited significance.

There are five pk studies examining interaction in those taking warfarin, atorvastatin, ramipril, dixogin, paracetamol and oral contraceptives. Since there is a delay in gastric emptying observed with this class of drugs, the timing of dosing of these drugs in relation to lixisenatide affected the pk. For example when paracetamol was administered 1 or 4 hours after lixisenatide, the tmax of paracetamol increased and the C_{max} decreased. This was also seen with the oral contraceptive interaction study.

Antibody status also affected the pk of lixisenatide. The incidence of antibody formation in healthy adult (multiple dose) studies and T2DM studies ranged from 30 – 60%. There was a five to seven fold increase in AUC with the 20 µg dose; there was also an increase in C_{max} (3-5 fold). The effects of these increases need to be examined in the Phase 3 studies.

4.6.2. Pharmacodynamic studies

Single dose studies showed an insulin response which was dose related in the 10 to 40 µg dose range in response to glucose challenge. Glucagon levels were not significantly changed in these studies.

In the Phase II studies there was a dose related effect in FPG, PPG, and other PD endpoints. This effect was seen in the range of 5- 40 µg.

Minimum effective dose in relation to FPG and PPG appear to be 5 µg. This would need review in the phase III studies based on HbA1c. Maximum tolerated dose is in the range of 20 -30 µg based on the Phase II studies and the PD endpoints.

There are studies that examined gallbladder motility and spermatogenesis on healthy volunteers. It does not provide evidence that these factors are not affected in diseased subjects.

The effect of lixisenatide on ventricular repolarisation did not show and significant abnormalities in healthy subjects. However, the sponsor is now undertaking a "thorough QT/QTc study" as per the adopted guidelines CHMP/ICH/2/04. The sponsor should inform the TGA when the results will be made available.[6]

In one 28 day study where the pd effects of lxisenatide (20mcg once a day) was compared to liraglutide 1.8 mg once day in T2DM, there was a statistically significant change favouring lixisenatide over liraglutide in relation to the primary PD endpoint- change in plasma glucose.

Body weight: Mean weight reduction compared with placebo (ACT6011) in lixisenatide 10 or 20 µg groups did not show any statistically significant difference over 28 days. PDY10931 showed a reduction at 28 days in the lixisenatide group (1.6 kg) and liraglutide group (2.4 kg).

[6] In the response to the CER, the sponsor commented that Study TES11807 has now been completed and the CSR is available upon request.

5. Dosage selection for the pivotal studies

There are 4 Phase II studies (ACT6011, DRI6012, PDY6797 and PDY 10931) included in this package. All these studies have been discussed in relation to pharmacology in the previous sections. Study DRI6012, is relevant for dose selection for the pivotal studies and is considered in detail below.

5.1. Study DRI6012

5.1.1. Design and objectives

This was a placebo-controlled, randomised, parallel-group dose response study in metformin treated T2DM subjects. There was a 2 week run-in and 13 weeks treatment period. The dose of lixisenatide used was 5 µg, 10 µg, 20 µg, or 30 µg either twice daily (before breakfast and before dinner) or once daily (before breakfast) ; subjects randomised to doses of 20 µg or 30 µg were to start with a dose of 10µg and escalate the dose in weekly 5 µg steps to the assigned dose.

The primary objective was to evaluate the dose-response relationship of lixisenatide administered once and twice daily in subjects with T2DM being treated with metformin. In this context, the primary efficacy endpoint was the change in HbA1c from baseline to week 13. Other endpoints analyses were plasma fructosamine, FPG, averages self monitored 7 point glucose, body weight and waist measurement.

Pharmacokinetic parameters and dynamic parameters have been discussed previously and will not be further considered.

Key inclusion criteria were males or females aged 30 – 75 years with T2DM, pre-treated with metformin at a stable dose of ≥ 1.0 g/day for at least 3 months prior to screening, with a body BMI of 25 - 40 kg/m^2 and an HbA1c of ≥ 7.0% and < 9.0% at screening. Those with significant medical conditions (including T1DM, the use of OAD other than metformin, insulin, significant medical illness, other medication use were excluded).

Randomisation and blinding methods and analysis populations were described.

Sample size: With 50 subjects in each active treatment and 100 in the combined placebo groups, there was 81% power to detect a difference of 0.6% in HbA1c between active treatment and placebo assuming an SD of 1.2%. While the study was adequately powered to detect a dose response, it was not adequately powered to detect any pair-wise dose comparisons between treatment arms at the alpha level of 0.05.

Participant flow: 542 subjects were randomised, 109 to placebo and 433 to lixisenatide. 489 subjects (90.2%) completed treatment and 53 discontinued the trial prematurely most commonly due to an adverse event (AE). This tended to be more frequent with higher doses of lixisenatide.

Baseline demographics: There were a total of 542 subjects randomised. The mean (sd) age was 56.17 (8.17) years; mean (sd) duration of diabetes was 6.62 (5.29) years and the mean (sd) duration of OAD intake was 4.89 (4.2) years. The study was well-balanced with regard to demographic characteristics including age, gender, race, duration of diabetes and metformin treatment, and daily metformin doses. At least 65% (range: 64.6 - 86.8%) of subjects in each group were Caucasian.

5.1.2. Results

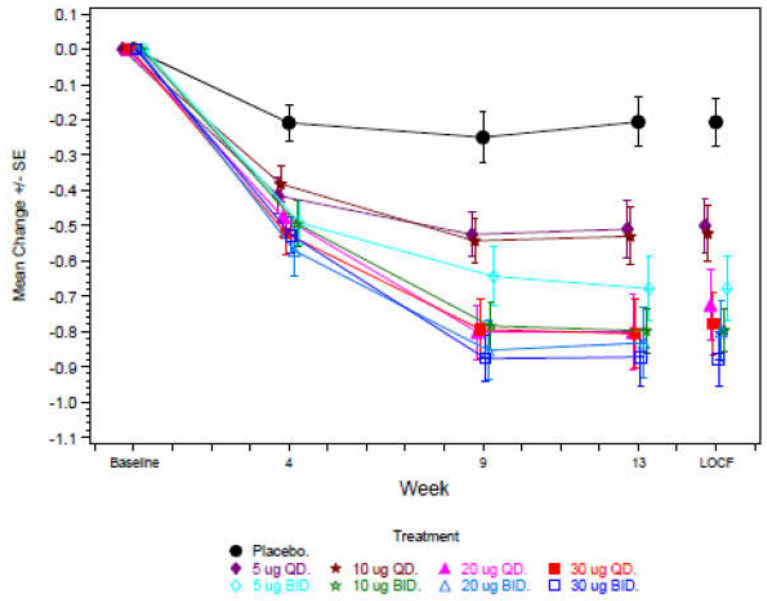
Primary efficacy variable:

Table 10: Mean change in HbA1c (%) from baseline to endpoint - ITT population

		AVE0010							
HbA1C (%)	Placebo (N=108)	5 µg QD (N=55)	10 µg QD (N=51)	20 µg QD (N=53)	30 µg QD (N=52)	5 µg BID (N=51)	10 µg BID (N=54)	20 µg BID (N=52)	30 µg BID (N=53)
Change									
N	107	55	50	53	51	51	54	52	53
Mean (SD)	-0.21 (0.71)	-0.50 (0.58)	-0.52 (0.55)	-0.73 (0.73)	-0.78 (0.63)	-0.68 (0.64)	-0.80 (0.44)	-0.80 (0.62)	-0.88 (0.55)
Median	-0.10	-0.40	-0.55	-0.80	-0.70	-0.70	-0.80	-0.80	-0.90
Min : Max	-2.5 : 2.6	-1.8 : 0.6	-1.8 : 0.8	-2.2 : 3.0	-2.7 : 1.0	-1.9 : 1.3	-1.7 : 0.2	-2.6 : 0.7	-2.1 : 0.4
LS Mean (SE)	-0.18 (0.073)	-0.47 (0.090)	-0.50 (0.095)	-0.69 (0.093)	-0.76 (0.094)	-0.65 (0.093)	-0.78 (0.091)	-0.75 (0.093)	-0.87 (0.095)
LS Mean difference (SE) vs. Placebo	-	-0.28 (0.097)	-0.31 (0.100)	-0.50 (0.098)	-0.57 (0.099)	-0.47 (0.099)	-0.59 (0.098)	-0.57 (0.099)	-0.69 (0.098)
95% CI	-	(-0.472 to -0.091)	(-0.508 to -0.115)	(-0.695 to -0.310)	(-0.768 to -0.377)	(-0.661 to -0.271)	(-0.784 to -0.401)	(-0.760 to -0.372)	(-0.878 to -0.492)
P-value*									
Step down linear trend test									
(QD)		0.0056	0.0033	<.0001	<.0001				
(BID)						<.0001	<.0001	<.0001	<.0001

The mean change from baseline over time (HbA1c (%) is graphically presented below.

Figure 1: Mean Change in HbA1c (%) by Visit and at Endpoint – ITT Population



There is a dose related change in the QD and BD treated groups. Whilst no '*a priori*' statistical comparison is factored between the active groups, 20 µg QD appears to produce a similar effect to 10 µg BD. This appears to produce optimum effect in relation to HbA_{1C}.

Results of analysis in the PP population reflected those of the ITT population.

Descriptive statistics for the change in HbA1c from baseline to endpoint by anti- lixisenatide Ab status are presented in the dossier. These show that median reductions in HbA1c were generally similar between anti- lixisenatide Ab+ve and –ve subjects for all doses except 30µg QD, where the median change was -0.9% for Ab +ve and -0.4% for Ab -ve subjects. However the results show a wide variability and general conclusions are limited regarding the effect of antibodies.

Secondary efficacy variables: In relation to endpoint HbA1c <6.5%, <7.0% or <7.5% there was dose-response relationship was seen for each regimen. There were no significant changes seen with bd or QD dosing.[7]

Body weight*:* There was a significant placebo effect i.e the mean (sd) weight loss was -1.51 kg (2.22) in the placebo group (n=108). With lixisenatide, the LS mean weight changes from baseline ranged from -2.00 kg (5µg QD) to -3.89 kg (30µg BID). The LS mean change compared to placebo with (95% CI) was -1.07 (-1.918 to -0.217) in the 20 µg QD group; it was -0.270 (-1.27- to 0.572) in the 10 µg bd group.

Waist circumference: It is noted that with the dose proposed for marketing, the LS mean difference (SE) vs placebo is -0.61cm (0.678); 20mcg QD was -.74 (0.669).

Changes in FPG, fructosamine and 7-point glucose were consistent with those for the primary efficacy variables with statistically significant differences compared to placebo for most lixisenatide doses, and, showed a dose response relationship.

Based on the change in Hb_{A1c} from baseline and the change in the secondary efficacy endpoints, the dose selection for the pivotal efficacy studies appears justified.

6. Clinical efficacy

The following table in relation to the efficacy data included the efficacy studies in support of the proposed indications. Whilst some studies have extension data for 76 weeks, the main efficacy analysis is performed at 24 weeks only. The studies will be dealt with according to the requested indications.

Table 11. Clinical Phase 3 studies in patients with T2DM: Completed studies as of 30 April 2011

Study (background treatment)	Primary objective	Lixisenatide dose (number of randomized patients)	Lixisenatide dose, form, regimen	Control (number of randomized patients)	Design	Treatment period
Pivotal studies						
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)
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)
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

[7] Sponsor clarification provided in the response to the CER: "There were no significant differences seen between bd or QD dosing."

6.1. Add on to metformin

There were three pivotal studies EFC 10743, EFC 6019 and EFC 6014. Of these, EFC 10743 and EFC 6014 are placebo controlled; EFC 6019 is active controlled (vs exenatide).

6.1.1. Placebo Controlled Studies

6.1.1.1. Study EFC6014:

6.1.1.1.1. Design and objectives

This was a randomised, double-blind, placebo-controlled, 4-arm, parallel-group, multi centre 24-week study followed by an extension assessing the efficacy and safety of lixisenatide as add on to metformin in patients with T2DM not adequately controlled with metformin. Patients who completed the 24 weeks of treatment entered into a double-blind, placebo-controlled extension period which was stopped when approximately 470 patients had been treated for at least 12 months.[8] The study was blinded in terms of the drug treatment (but not blinded in relation to drug volume or time of injection).

Primary objective: To assess the efficacy of lixisenatide on glycaemic control when it is used in the morning within 1 hour prior to the meal in comparison to placebo as an add-on treatment to metformin, in terms of HbA1c reduction (absolute change) over a period of 24 weeks in patients withT2DM. In this context, the primary efficacy endpoint was the change from baseline in HbA1c.

There were several **secondary efficacy variables**: 2 hour PPG (mmol/L) after a standardised meal[9]; body weight (kg); FPG (mmol/L); fasting plasma insulin (pmol/L); beta cell function assessed by HOMA-β;adiponectin; glucose excursion after a standardised meal (morning injection arms only); glucagon (ng/mL, proinsulin (pmol/L), plasma insulin, % of patients requiring rescue therapy. There were also secondary beta cell function variables.

Main inclusion criteria: Patients with T2DM diagnosed at least 1 year before the screening visit; insufficiently controlled with metformin (at a stable dose of at least 1.5 g/day for at least 3 months prior to screening); and HbA_{1c} ≥ 7.0% and ≤ 10% at screening. Exclusion criteria were comprehensive.

Study treatments: After a 1-week placebo run-in phase with 10µg QD placebo injections, patients were randomised to 1 of the following treatments:

- Lixisenatide or lixisenatide volume-matched placebo injection in the morning.
- Lixisenatide or lixisenatide volume-matched placebo injection in the evening.

Study treatment was self-administered by SC injections QD within the hour preceding breakfast or dinner alternating between abdominal wall, thighs and upper arms. The starting dose of lixisenatide was 10µg. The lixisenatide formulation was 100µg/mL. This was up titrated to 15 and 20µg as tolerated over 2 weeks pending safety and tolerability. A standardised meal challenge test was undertaken by all patients prior to treatment, patients who received morning injections at the last study visit of the main treatment period, and, in some patients who received morning injections 4 weeks after the end of treatment.

Metformin was to be continued at a stable dose throughout the study.

[8] Sponsor clarification, provided in the response to the CER: Further to a protocol amendment, the patient completion date was changed. The sentence should therefore read: "Patients who completed the 24 weeks of treatment entered into a double-blind, placebo-controlled extension period which was stopped approximately at the last scheduled date of week 76 visit for the last randomised patient."

[9] Sponsor clarification, provided in the response to the CER: 2 h PPG was only measured in the morning injection arm, but not in the evening injection arm.

Randomisation and blinding methods, analysis populations and statistical methods: Randomisation was stratified by screening HbA1c (<8.0%, ≥ 8.0%) and BMI (<30 kg/m^2, ≥ 30 kg/m^2).

Sample size: The sample size calculations were based on the primary efficacy endpoint, change from baseline to week 24 in HbA_{1c}. It assumed a common SD of 1.3% with a 2-sided test at the 5% significance level and was based upon the 2-sample t test. A sample size of 255 patients for each lixisenatide arm and 2 x 85 patients for the combined placebo group was considered sufficient to detect a difference of 0.5% (or 0.4%) in the absolute change in HbA1c from baseline to Week 24 between lixisenatide and placebo, with a power of 97% (or 87%). Thus, this a superiority study.

Subject disposition: 680 patients were randomised to 1 of the 4 treatment groups, 255 patients in both the morning and evening lixisenatide groups and 85 patients in both the morning and evening placebo groups. Information on discontinuations in the 24 week and extension periods and status at the last patient contact is presented in the dossier.

Protocol deviations: No patients were excluded from the mITT efficacy analysis due to a protocol deviation. The blind was broken for 6 patients receiving lixisenatide due to serious adverse events (SAEs). Treatment was unblinded for 1 placebo patient with signet-ring cell carcinoma, which led to permanent discontinuation from the study.

Baseline data: All randomised subjects (n=680) were included in the mITT analysis and safety analysis. 335/680 was included in the pk analysis. Data are provided showing that the demographic and patient baseline characteristics were generally similar across treatment groups for the safety population. The mean (sd) age was 54.7 years (9.7); 56.9% were females; 88.8% were Caucasians and 7.8% were Asians and Orientals; baseline HbA_{1c} was 8.17% (0.85); 50.6% had a baseline HbA_{1c} ≥ 8%; BMI was 33.6 kg/m^2(6.36). The median duration of metformin therapy for patients in the combined lixisenatide group was 2.35 years and the median dose of metformin was 2000mg per day.

Treatment compliance: (97.6%) treated with lixisenatide and (98.8%) treated with placebo having a compliance of between 80% and 100%.

6.1.1.1.2. Results

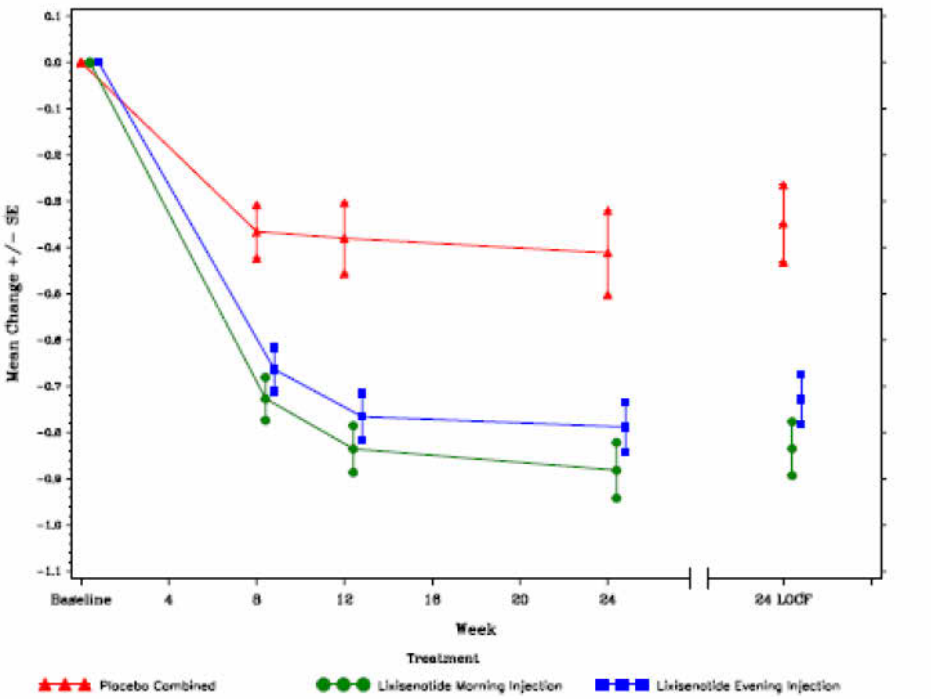
Primary efficacy variable*:* The results are tabulated below.

Table 12: Mean change in HbA1c (%) from baseline to Week 24 - mITT population

		Lixisenatide	
HbA1c (%)	Placebo Combined (N=170)	Morning Injection (N=255)	Evening Injection (N=255)
Baseline			
Number	164	244	239
Mean (SD)	8.02 (0.89)	8.07 (0.90)	8.07 (0.89)
Median	7.80	8.00	7.90
Min : Max	6.4 : 10.5	5.3 : 12.0	6.5 : 10.2
Week 24 (LOCF)			
Number	164	244	239
Mean (SD)	7.67 (1.08)	7.24 (0.99)	7.34 (1.04)
Median	7.55	7.10	7.10
Min : Max	5.2 : 13.8	5.1 : 11.0	5.4 : 11.7
Change from baseline to Week 24 (LOCF)			
Number	164	244	239
Mean (SD)	-0.35 (1.06)	-0.83 (0.91)	-0.73 (0.84)
Median	-0.30	-0.90	-0.70
Min : Max	-3.6 : 5.8	-3.3 : 2.9	-3.0 : 2.5
LS Mean (SE) [a]	-0.38 (0.075)	-0.87 (0.065)	-0.75 (0.066)
LS Mean difference (SE) vs. placebo combined [a]		-0.48 (0.088)	-0.37 (0.088)
95% CI		(-0.657 to -0.312)	(-0.540 to -0.193)
p-value		<0.0001	<0.0001

These results show that the LS mean reduction from baseline to Week 24 in HbA1c was greater in both morning and evening lixisenatide groups than in the combined placebo group. The figure below shows the mean (± SE) change from baseline in HbA1c over time during the main 24-week double-blind treatment period.

Figure 2: Plot of mean change in HbA1c (%) from baseline by visit up to Week 24 - mITT population



Secondary efficacy variables: Percentage of patients with HbA1c responders*:* The percentage patients with HbA1c ≤ 6.5% or < 7% at week 24 was higher with morning lixisenatide (23.8% and 43.0%, respectively) and with evening lixisenatide (19.2% and 40.6%, respectively) compared with the combined placebo group (10.4% and 22.0%, respectively).

Body weight*:* The reduction from baseline to week 24 was similar with morning and evening lixisenatide (LS mean change -2.01 and -2.02 kg, respectively). The LS mean change was -1.64 kg for the combined placebo group. This was not statistically significant.

Rescue therapy*:* Lower percentages of patients required rescue therapy in both lixisenatide groups during the 24-week treatment period (2.7% for morning and 3.9% for evening injection) compared with the combined placebo group (10.6%). During the entire study, 23.1%, 20.8%, and 32.9% of patients in the morning and evening injection lixisenatide groups, and in the combined placebo group, respectively, required rescue therapy.

Results for other secondary efficacy variables were consistent with those of HbA_{1c} reduction and responder rates. A summary of results for PPG and glucose excursion, FPG, β-cell function, fasting plasma insulin, adiponectin levels, meal-related glucagon, insulin, proinsulin, and C-peptide, and, secondary efficacy results 4 weeks after treatment discontinuation are presented in the dossier.

The extension period efficacy data were evaluated by descriptive statistics only and will not be considered further.

The evaluator could not locate data on the antibody status and the relationship to efficacy results.[10]

6.1.1.2. Study EFC10743

6.1.1.2.1. Design

This was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, 24-week study followed by an extension assessing the efficacy and safety of lixisenatide with 2- and 1-step titration regimens in addition to metformin in patients with T2DM not adequately controlled with metformin. The titration processes were:- a two step process- 10 µg (QD) for one week followed by 15 µg (QD) for one week then followed by a 20 µg (QD) as maintenance dose. The one step process had 10 µg (QD) for two weeks followed by the 20 µg (QD) maintenance dose. The extension phase stopped for all patients when approximately 300 patients in total (around 150 patients in each titration regimen) had been treated for at least 12 months.[11]

Those with the $HbA_{1c} \geq 7.0\%$ and $\leq 10\%$ at screening were eligible to enrol. Other design and study conduct details were similar to the previous study.

484 patients were randomised as follows: 161 in both lixisenatide titration groups; 80 in the placebo 2-step titration group and 82 in the placebo 1-step titration group.

482 patients were exposed to the study treatment and included in the analysis as 2 patients randomised to the placebo titration groups did not receive treatment. Data on the patient disposition were provided.

Baseline data: Mean age (sd) was 56.1 (9.3) years; there were 44.9 % females; Caucasians were 90.2% and Asians 6.9%. Mean HbA_{1c} was 8.16% (0.84) and those with $HbA_{1c} < 8$ was 48.2%; mean BMI was 32. 53 kg/m^2. Data are provided showing that the demographic and patient baseline characteristics were generally similar across the treatment groups for the safety population. The median metformin dose (mg/day) was 1700 mg and 2000 mg in the combined placebo and lixisenatide groups respectively.

6.1.1.2.2. Results

Treatment compliance was good, with 315 patients (97.8%) treated with lixisenatide and 156 patients (97.5%) treated with placebo having a compliance of 80 - 100%. Of the 482 randomised and treated patients, 3 patients (1 patient with lixisenatide 2-step and 1-step titration and 1 patient with placebo 1-step titration) were excluded from the mITT population for efficacy analyses due to lack of post baseline efficacy data. Subject disposition data are included in the dossier.

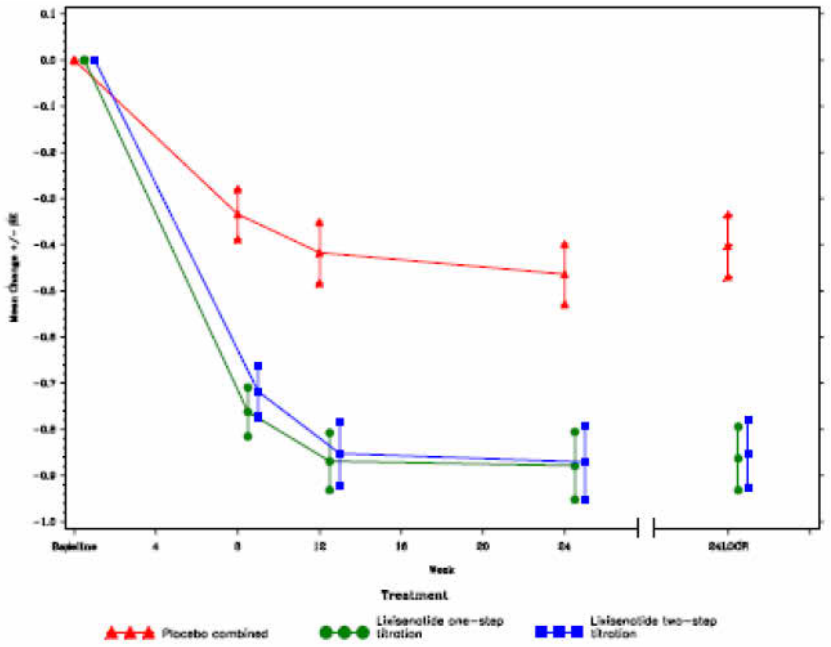
[10] Sponsor clarification, provided in the response to the CER: This analysis was not available at the time of the initial submission, but was subsequently completed. An amended version of the CSR incorporating this data is available upon request

[11] Sponsor clarification, provided in the response to the CER: Further to a study protocol amendment the patient completion date was changed. This sentence should read as follows: "The extension phase stopped for all patients approximately at the scheduled date of week 76 visit for the last randomised patient"

Table 13: EFC10743. Primary efficacy variable

HbA1c (%)	Placebo Combined (N=159)	Lixisenatide Two-step Titration (N=160)	Lixisenatide One-step Titration (N=160)
Change from baseline to Week 24 (LOCF)			
Number	158	152	156
Mean (SD)	-0.40 (0.85)	-0.85 (0.93)	-0.86 (0.86)
Median	-0.40	-0.80	-0.80
Min : Max	-3.1 : 2.2	-4.0 : 2.4	-3.8 : 1.3
LS Mean (SE) [a]	-0.42 (0.099)	-0.83 (0.099)	-0.92 (0.101)
LS Mean difference (SE) vs. placebo combined [a]	-	-0.41 (0.089)	-0.49 (0.090)
95% CI	-	(-0.583 to -0.232)	(-0.670 to -0.317)
p-value		<.0001	<.0001

Figure 3: EFC10743. Primary efficacy variable



As seen above, there were statistically significant changes seen with the active in comparison to placebo. The study was not statistically powered to detect a difference between the two active treatment regimen group. The mean change in HbA1c by BMI (< 30 or ≥30) or by HbA1c category (<8% or ≥ 8%) was similar. The effect of race was diffciult to assess as the numbers who were not Caucasians were small.

There is some information of the presence of antibodies and the HbA_{1c}:

Table 14: Mean change in HbA1c (%) from baseline to week 24 by anti-lixisenatide Ab status prior to rescue and/or at week 24 - mITT population

	Lixisenatide							
	Two-step Titration (N=160)				One-step Titration (N=160)			
	N	Mean (SD)	LSMean (SE)[a]	95% C.I.[a]	N	Mean (SD)	LSMean (SE)[a]	95% C.I.[a]
Anti-Lixisenatide antibody status prior to rescue and/or at Week 24								
Positive	102	-0.82 (0.91)	-0.82 (0.110)	(-1.037 to -0.606)	109	-0.84 (0.80)	-0.93 (0.112)	(-1.154 to -0.713)
Negative	36	-0.92 (1.08)	-0.91 (0.160)	(-1.223 to -0.595)	36	-0.94 (1.08)	-0.92 (0.159)	(-1.234 to -0.610)

Table 15: Mean change in HbA1c (%) from baseline to Week 76 by anti-lixisenatide Ab status prior to rescue and at Week 76 - mITT

	Lixisenatide											
	Two-step Titration (N=160)						One-step Titration (N=160)					
	N	Mean	SD	SE	Median	95% CI for mean	N	Mean	SD	SE	Median	95% CI for mean
Anti-Lixisenatide antibody status prior to rescue and at Week 76												
Positive	59	-0.81	0.89	0.115	-0.70	(-1.036 to -0.574)	58	-0.76	0.83	0.109	-0.70	(-0.980 to -0.544)
Negative	27	-1.23	1.08	0.208	-1.10	(-1.654 to -0.798)	30	-1.11	0.99	0.182	-1.20	(-1.482 to -0.738)

The results show wide variation in HbA_{1c} values and make it difficult to interpret. However, it is noted that at 24 weeks, the decrease in HbA_{1c} was 0.10% less with both titration groups in Ab+ve patients compared to the Ab-ve patients.

Secondary efficacy variables*:* The results are in line with those observed with the primary endpoint. It is noted that The LS mean reduction in body weight from baseline to week 24 was similar with lixisenatide 2-and 1-step titration (-0.68 kg[12] and -2.63 kg respectively) and was -1.63 kg for the combined placebo group.

The evaluator notes the following: In the data on HbA1c change from baseline by Ab status, there were fewer patients in both lixisenatide 2-and 1-step titration treatment groups (138 and 145 respectively) than in the efficacy analysis (152 and 156 respectively). This is different to the numbers in the safety results which shows Ab status at 24 weeks in 140 and 143 patients in the 2- and 1-step titration groups respectively. In addition the safety data show that 22/30 (76.7%) patients in the 2-step and 28/36 (77.8%) in the 1-step titration groups were Ab+ve prior to rescue therapy.

6.1.2. Studies with active comparators

6.1.2.1. Study EFC6019

6.1.2.1.1. Design

This was a randomised, open-label, active-controlled, 2-arm parallel-group, multi centre 24-week study followed by an extension period assessing the efficacy and safety of lixisenatide versus exenatide as add on to metformin in patients with T2DM not adequately controlled with metformin. The extension period ended for all patients at around week 76 of treatment for the last randomised patient.

[12] Erratum: correct value is -2.68 kg.

Objectives: Primary: To assess the efficacy of lixisenatide on glycaemic control when it is used [once a day] in the morning within 1 hour prior to the meal in comparison to exenatide [twice a day] (Byetta) as an add-on treatment to metformin in terms of HbA_{1c} reduction (absolute change) over a period of 24 weeks in patients with T2DM. In line with this the primary efficacy endpoint was change in HbA_{1c} from baseline.

Secondary*:* Percentage of patients reaching HbA1c < 7% or ≤ 6.5%**,** FPG**,** body weight; lixisenatide safety and tolerability*;* the impact of gastrointestinal tolerance on quality of life (QoL) (patient assessment of upper gastrointestinal disorders - quality of life [PAGI-QOL]).

Main inclusion criteria was as per previous studies i.e patients with T2DM diagnosed at least 1 year before the screening visit; receiving metformin treatment at a stable dose of at least 1.5 g/day for at least 3 months prior to screening; and HbA_{1c} ≥ 7.0% and ≤ 10% at screening. Exclusion criteria were similar to those of the previous studies.

Study treatments: Lixisenatide was self-administered SC, QD within the hour preceding breakfast. The dosage schedule was 10µg QD for 1 week, then 15µg QD for 1 week followed by the maintenance dose of 20µg QD up to the end of the treatment period. The lixisenatide formulation was 100µg/mL.

The active comparator, exenatide, was self-administered by SC, BID within the hour preceding breakfast and within the hour preceding dinner. The dosage schedule was 5µg BID of exenatide for 4 weeks, then 10µg BID for the remaining treatment period.

Randomisation was as per previous studies.

This was designed as a non inferiority trial. The predefined non inferiority margin was 0.4% HbA1c. Non inferiority was demonstrated if the upper bound of the 2-sided 95% CI of the difference in the adjusted mean change in HbA1c from baseline to week 24 between lixisenatide and exenatide in the mITT population was ≤ 0.4%. A sample size of 600 subjects (300 subjects in each group) was required to demonstrate this. The non-inferiority margin appears wide especially as this magnitude or 0.5% has been used to establish superiority over placebo.

Participant flow: 639 patients were randomised. 5 randomised patients were excluded from all efficacy and safety analyses due to serious non-compliance with the protocol at one site. 17 patients from the 2 other non-compliant sites were not excluded as the non-compliance was considered less serious. Hence, 634 patients were included in the analyses, 318 receiving lixisenatide and 316 receiving exenatide. A summary of patient disposition for the 24 week and extension periods is provided in the dossier.

Major protocol deviations: There were no other deviations leading to exclusion from the mITT population.

Baseline data: The populations analysed are presented below. 3 patients with lixisenatide and 1 patient with exenatide were excluded from the mITT population for efficacy analyses due to lack of post baseline efficacy data.

Baseline demographics: The mean age (sd) in the lixisenatide group was 57.3 (9.2) vs 57.6 (10.7) in the exenatide group; males – 47.% vs 59.2%; mean baseline HbA1 c 8.03 (0.8) vs 8.02 (0.78) respectively; those with HbA_{1c} ≥ 8 was 46.9% vs 46.5%; mean BMI was 33.6 (6.2) vs 33.5 (6.5). The majority of the patients were Caucasian (92.7%). The median duration of metformin treatment was 2.49 years with lixisenatide and 2.90 years with exenatide. All patients were treated with ≥ 1500 mg of metformin per day. Baseline HbA_{1c} and FPG at were generally comparable between the 2 treatment groups. However there was a baseline imbalance in mean body weight between the 2 treatment groups (94.51 kg in the lixisenatide tretament group and 96.69 kg in the exenatide group, mITT population.

Treatment compliance was 80-100% in 311 (97.8%) patients receiving lixisenatide and 303 (95.9%) receiving exenatide.

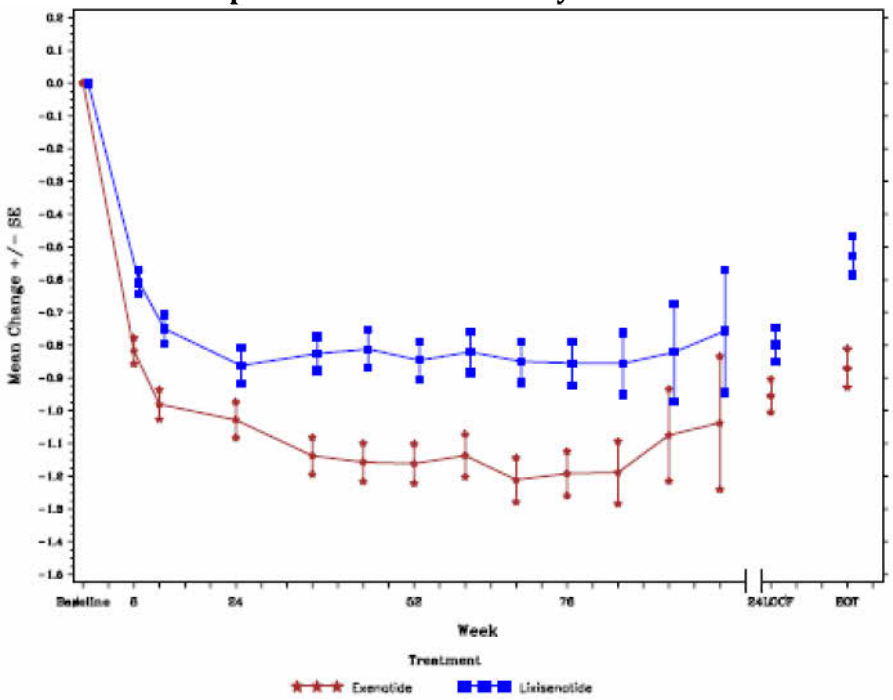
Primary efficacy variable: The LS mean change from baseline to Week 24 in HbA_{1c} was -0.79% with lixisenatide and -0.96% with exenatide. The LS mean difference versus exenatide was 0.17%; (95% CI: 0.033, 0.297). Non inferiority of lixisenatide versus exenatide was demonstrated as the upper bound of the 2-sided 95% CI of the LS mean difference was < 0.4%. Superiority of lixisenatide over exenatide was not demonstrated.

Table 16: Mean change in HbA1c (%) from baseline to week 24 - mITT population

HbA1c (%)	Lixisenatide (N=315)	Exenatide (N=315)
Change from baseline to week 24 (LOCF)		
Number	295	297
Mean (SD)	-0.80 (0.88)	-0.95 (0.87)
Median	-0.80	-0.90
Min : Max	-3.1 : 3.8	-3.3 : 3.4
LS Mean (SE) [a]	-0.79 (0.053)	-0.96 (0.054)
LS Mean difference (SE) vs. Exenatide [a]	0.17 (0.067)	
95% CI	(0.033 to 0.297)	

Mean change in HbA_{1C} over time is presented below. This shows that in both treatment groups the HbA_{1c} reduction was relatively maintained over the main 24-week on-treatment and extension periods.

Figure 4: CSR EFC6019: Plot of mean change in HbA1c (%) from baseline by visit during the on-treatment period of the whole study – mITT



Results of the sensitivity analyses to assess the impact of rescue medication were consistent with the primary analysis of the data.

Secondary efficacy variables. Percentage of patients with HbA1c ≤ 6.5% or <7% at Week 24*:* At week 24, 28.5% of patients with lixisenatide and 35.4% with exenatide had HbA1c values ≤ 6.5%.

48.5% with lixisenatide and 49.8% with exenatide had achieved values < 7%. This is tabulated below.

Table 17: Number (%) of patients with HbA1c ≤ 6.5% or <7% at Week 24 - mITT population

HbA1c (%)	Lixisenatide (N=315)	Exenatide (N=315)
Number	295	297
≤6.5%	84 (28.5%)	105 (35.4%)
Proportion difference (95% CI) vs. Exenatide[a]	-6.6% (-13.9% to 0.60%)	-
Number	295	297
<7.0%	143 (48.5%)	148 (49.8%)
Proportion difference (95% CI) vs. Exenatide[a]	-1.0% (-8.51% to 6.51%)	-

[a] Based on the fixed effect meta-analysis method using Cochran-Mantel-Haenszel (CMH) weights stratified by randomization strata of screening HbA1c (<8.0 or ≥ 8.0 %) and screening BMI (<30 or ≥ 30 kg/m²). Proportion difference = difference of the proportions of patie achieving HbA1c value ≤6.5% or <7% respectively.

Results for the other secondary efficacy variables: For FPG, the LS mean change from baseline to week 24 was -1.22mmol/L for the lixisenatide treated group and -1.45 mmol/L for the exenatide group (LS mean difference vs exenatide was 0.23 mmol/L). The percentage of patients requiring rescue therapy during the 24 week tretament period was 2.2% and 3.8% in the lixisenatide and exenatide groups respectively.

The LS mean body weight loss from baseline at week 24 was 2.96 kg for the lixisenatide group and 3.98 kg for the exenatide treated group. Approximately 25.5% of the lixisenatide treated group and 31.4% of the exenatide treated group had a weight loss ≥ 5% of weight loss.

The effects relating to HbA_{1c}, FPG and bodyweight were maintained during the extension period.

Though non-inferiority was seen in relation to pre-defined endpoints, exenatide showed a magnitude greater than lixisentide in relation to the primary efficacy endpoint; superior trends were also observed with exenatide in relation to the secondary endpoints, including weight loss. The margin for non-inferiority was also wide and should have been of narrower magnitude.

There was no antibody testing performed in this study.

6.1.2.2. Study EFC10780

This study is considered supportive as its primary objective is to assess a composite endpoint of HbA_{1c} and body weight in subjects who are 50 years and under. Claims relating to this are not advocated in the PI and, hence, this has supportive information only.

6.1.2.2.1. Design

This was a randomised, double-blind, double-dummy, active comparator-controlled, 2-arm, balanced, parallel-group, multicentre, multinational 24-week study comparing the efficacy and safety of lixisenatide to sitagliptin as add-on to metformin in obese T2DM patients aged < 50 years and not adequately controlled with metformin.

Objectives: Primary*:* To assess the efficacy of lixisenatide on a composite endpoint of glycaemic control, HbA_{1c} and body weight, in comparison to sitagliptin as an add-on treatment to metformin, over a period of 24 weeks in obese T2DM patients < 50 years of age.

Secondary: To assess the effects of lixisenatide on: absolute changes in HbA1c values, body weight and FPG; plasma glucose, insulin, C-peptide, glucagon, and pro-insulin during a 2-hour standardised meal test; insulin resistance assessed by homeostatic model assessment of insulin resistance (HOMA-IR); beta cell function assessed by HOMA-β; lixisenatide safety and tolerability, and, anti-lixisenatide Ab development.

Inclusion and exclusion criteria were similar to previous studies; the age of those recruited was less than 50 years.

Study treatments: The study treatments were:

- Lixisenatide: 10µg QD for 1 week, then 15µg QD for 1 week followed by the maintenance dose of 20µg QD up to the end of the treatment period.
- Sitagliptin: 100 mg orally QD throughout the treatment period.

The **primary efficacy endpoint** was the percentage of patients with HbA1c <7.0% AND a weight loss of at least 5% of baseline at week 24.The secondary variables reflected the secondary objectives mentioned above.

Subject disposition: 319 patients were randomised with 158 and 161 patients in the lixisenatide and sitagliptin groups respectively. All were exposed to the study treatment and included in the analyses. The number of patients who prematurely discontinued was low. More patients discontinued with lixisenatide (16 [10.1%]) than with sitagliptin (11 [6.8%]). Treatment was discontinued at the patient's request for 22 of these 27 patients. In both groups, the main reason for discontinuation was "other reasons" (4.4% and 3.1% with lixisenatide and sitagliptin, respectively), followed by "AE" (2.5% and 3.1% with lixisenatide and sitagliptin respectively).

Baseline data: The mean age (sd) of the study participants randomised was 43.1 (4.9) years; there were 40.1% males; 81.2% were Caucasians; mean HbA1c was 8.27 %; those with HbA1c ≥ 8 was 58.9%; BMI was 36.86kg/m^2 (6.78).

Primary efficacy variable*:* The percentage of patients with HbA1c < 7.0% AND a weight loss of at least 5% of baseline body weight at week 24 was (19 patients [12.0%]) with lixisenatide and with sitagliptin (12 [7.5%]). The weighted average difference in response rate for lixisenatide versus sitagliptin was 4.6% (95% CI: -1.84%, 11.00%; p = 0.1696). Based on the prespecified primary analysis (see sample size/power calculation above), no statistically significant difference was seen between the 2 treatment groups.

The **secondary efficacy endpoints**: There was a statistically significant difference in body weight loss with lixisenatide at week 24; -2.51 kg compared with -1.17 with sitagliptin. This is of limited significance as there is no claim to weight loss in the sitagliptin PI.

6.2. Add on to sulfonylurea +/- metformin

Two studies (EFC 6015 and PDY 6797) are submitted. These studies are to support the use with sulfonylurea (as dual therapy) or together with metformin (as triple therapy).

6.2.1. Study EFC6015

6.2.1.1. Design

This was a randomised, double-blind, placebo-controlled, 2-arm, unbalanced design, parallel-group, multicentre 24-week study with an extension assessing the efficacy and safety of lixisenatide in patients with T2DM not adequately controlled with sulfonylurea (with or without metformin). The extension was stopped for all patients when approximately 600 patients have been treated for at least 12 months.[13]

Objectives: Primary: To assess the effects of lixisenatide on glycaemic control in comparison to placebo as an add-on treatment to sulfonylurea, without or with metformin, in terms of absolute HbA_{1c} reduction over a period of 24 weeks in patients with T2DM.Thus, the change in HbA_{1c} was

[13] Sponsor clarification, provided in the response to the CER: Further to a study protocol amendment the patient completion date was changed. This sentence should read as follows: "The extension phase ended for all patients at week 76 visit of the last randomised patient"

the primary efficacy endpoint. The secondary efficacy endpoints were similar to the other pivotal studies; in addition, the safety, tolerability and pk of lixisenatide and anti-lixisenatide Ab development.

Main inclusion criteria: Patients with T2DM diagnosed at least 1 year before the screening visit, insufficiently controlled with a sulfonylurea alone (at a stable dose for at least 3 months prior to screening) or a sulfonylurea in association with metformin at a stable dose of at least 1.5 g/day (except at least 0.75 g/day in Japan and 1.0 g/day in South Korea) for at least 3 months prior to screening), and HbA1c ≥ 7.0% and ≤ 10% at screening. Exclusion criteria were broadly similar to other pivotal studies.

Study treatments: The starting dose was 10µg lixisenatide or volume-matched placebo. The dose was increased after one week to 15µg and after one more week from 15 to 20µg pending patient safety and tolerability. In patients with screening HbA1c < 8%, the sulfonylurea dose was decreased by 25-50% at the baseline visit to prevent possible hypoglycaemia. It was then gradually increased to the dose at screening (or maximally effective tolerated dose) between week 4 and 12 according to glucose measurements. It was not changed after week 12 unless there was a safety issue. For patients on metformin at screening, the metformin dose was kept stable throughout the study.

Sample size calculations were based on the primary efficacy endpoint as in previous studies. A sample size of 570 in the lixisenatide and 285 in the placebo group) were considered sufficient to detect a difference of 0.5% (or 0.4%) in the absolute change in HbA1c from baseline to week 24 between lixisenatide and placeb0 (with a power of 99%). This was a superiority study. There were several subgroup analyses planned. Of importance was the use (or not) of metformin.

Efficacy variables and endpoints: The efficacy variables and endpoints reflect the objectives.

Randomisation was stratified by screening HbA_{1c} (< 8.0%, ≥ 8.0%) and screening for metformin use (yes, no).

Subject disposition: 859 patients were randomised, 573 to lixisenatide and 286 to placebo. All were exposed to study treatment. 499 (87.1%) patients receiving lixisenatide and 255 (89.2%) receiving placebo completed the main 24-week treatment period. 396 (69.1%) receiving lixisenatide and 204 (71.3%) receiving placebo completed the overall treatment period.

The most common reasons for treatment discontinuation were AEs and lack of efficacy. It is stated that 468 patients (313 and 155 with lixisenatide and placebo respectively) participated in the meal challenge test.

Baseline data: Data are provided showing that the demographic and patient baseline characteristics were generally similar between the 2 treatment groups for the safety population. The median age was 58.0 years. 52.2% of the patients were Caucasian and 44.8% were Asian. The mean (sd) HbA_{1c} was 8.36% (0.82) at baseline. The proportions with HbA1c < 8% were about 35% in both groups. The median duration of T2DM in the lixisenatide group was 7.99 years. All were on a sulfonylurea for a median duration of 4.44 years. The majority were on glimepiride (42.6%) at a mean dose of 5.1/day, glibenclamide (24.9%) at a mean dose of 12.9mg/day; others used were gliclazide, glipizide, gliquidone and tolbutamide. 86.4% of patients were receiving metformin at baseline for a median duration of 4.10 years and a median dose of 2000mg/day. The mean (sd) baseline BMI was 30.22 kg/ m^2 (6.22).

Other baseline data were presented in the dossier.

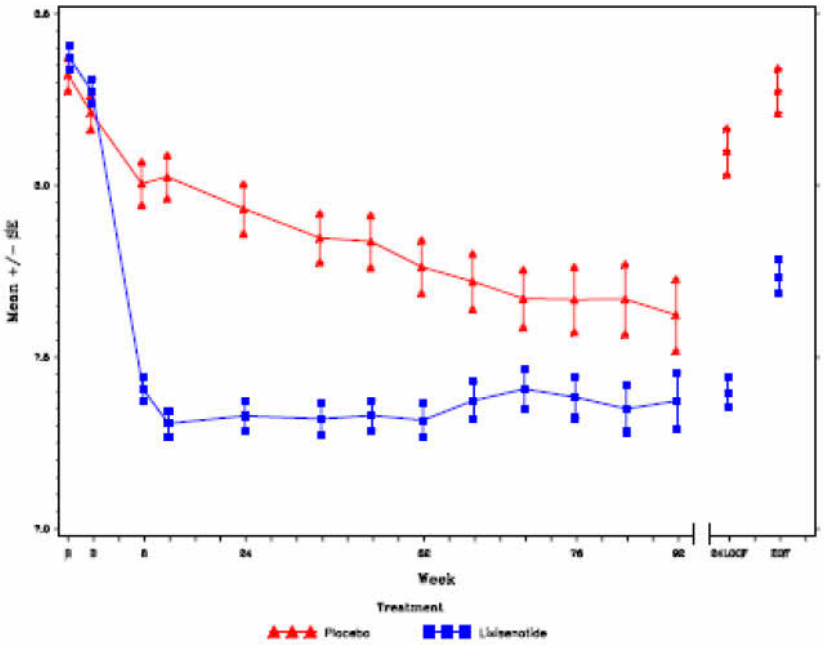
6.2.1.2. Results

Treatment compliance was good, with 557 (97.0%) patients receiving lixisenatide and 281 (98.6%) receiving placebo having a compliance of 80-100%.

Primary efficacy variable: The LS mean change from baseline to week 24 in HbA_{1c} was -0.85% with lixisenatide and -0.10% with placebo (LS mean difference versus placebo: -0.74%; 95% CI:

-0.867, -0.621). The LS mean difference of lixisenatide versus placebo was statistically significant, p<0.0001. The figure below shows the mean (±SE) change from baseline in HbA_{1c} over time during the total on-treatment period.

Figure 5: Plot of mean change in HbA1c (%) from baseline by visit - mITT population



The maximum HbA_{1c} reduction was observed in the first 12 weeks of treatment for both groups and then maintained. It was greater with lixisenatide compared with placebo. It appears that the placebo arm (sulfonylurea ± metformin) had sustained effect.

A sensitivity analysis to assess the impact of rescue medication on mean change in HbA1c reduction from baseline to week 24 supported the main analysis.

Data provided on the mean change in HbA1c from baseline to week 24 by baseline factor and by country showed that the largest difference in the LS mean for lixisenatide versus placebo was demonstrated in Japan (-1.16), whereas other Asian countries were in line with non-Asian countries. The LS mean difference for lixisenatide versus placebo was greater in Asians than Caucasians (-0.93 and -0.61, respectively). The LS mean difference also appeared to be higher in Hispanic than non Hispanic patients (-1.02 versus -0.74, respectively), but the analysis was limited by small numbers, 18 patients (3.2%) with lixisenatide and 5 (1.7%) with placebo. Too few black patients were recruited for a meaningful analysis in this subgroup.

The mean change in HbA_{1c} from baseline to Week 24 by baseline factor also showed a higher LS mean difference for lixisenatide in:

- Males compared to females (-0.82 versus -0.66, respectively).
- Patients with baseline HbA1c ≥ 8% compared to those with baseline HbA1c < 8% (-0.89 versus -0.52, respectively).
- Patients with baseline BMI < 30 kg/m^2 compared to those with baseline BMI ≥ 30 kg/m^2 (-0.83 versus -0.64, respectively).

For patients who used metformin at screening, the LS mean difference for lixisenatide versus placebo was -0.72 (95% CI: -0.857, -0.591), and for those who did not use metformin at screening it was -0.85 (95% CI: -1.161, -0.543).The number not using metformin at baseline was 16%. This is the subset that this study provides as support for “add on therapy with sulfonylurea”.

The mean change in HbA1c from baseline to Week 24 by anti-lixisenatide Ab status and concentration is presented in the table below. Concentration is highest in the 4th quartile.

Table 18: Mean change in HbA1c (%) from baseline to Week 24 by anti-lixisenatide Ab status and concentration - mITT population

	Lixisenatide (N=570)			
	N	Mean (SD)	LSMean[a] (SE)	95% C.I.[a]
Anti-Lixisenatide antibody status prior to rescue and/or at Week 24				
Positive	207	-0.86 (0.95)	-0.79 (0.084)	(-0.959 to -0.630)
Negative	135	-0.90 (0.93)	-0.79 (0.096)	(-0.974 to -0.597)
Anti-Lixisenatide antibody concentration (nmol/L) prior to rescue and/or at Week 24				
<LLOQ	179	-1.00 (0.93)	-0.79 (0.095)	(-0.979 to -0.605)
1st quartile	23	-0.87 (1.04)	-0.55 (0.190)	(-0.923 to -0.176)
2nd quartile	23	-0.30 (1.21)	-0.08 (0.185)	(-0.441 to 0.288)
3rd quartile	23	-0.43 (0.68)	0.03 (0.187)	(-0.340 to 0.399)
4th quartile	23	-0.43 (0.75)	-0.07 (0.196)	(-0.456 to 0.314)

It is considered that there were no relevant differences between Ab+ve and –ve patients. However, it is noted that the mean reduction seemed to be somewhat smaller with increasing Ab concentration. Week 76 data are provided showing that the mean reduction in HbA1c was lower in Ab+ve patients. However, the reduction in patients with the highest Ab concentrations did not differ from that of patients with low concentrations. It is noted that this analysis is limited by the small number of patients in each concentration quartile.

Secondary efficacy findings reflected the primary efficacy findings and are included in the dossier. Data are provided showing that the effects on the secondary efficacy variables, FPG, 2-hour PPG, and body weight observed during the main 24-week treatment period were maintained during the variable extension period.

6.2.2. Study PDY6797

This is a supportive study as it is a Phase 2 dose escalation study conducted on Caucasian and Japanese patients.

6.2.2.1. Design

This was a randomised, double-blind, placebo-controlled, multinational study evaluating the safety and pk of 5 µg and 10µg lixisenatide single doses, and the efficacy, safety and pk of lixisenatide administered for 5 or 6 weeks, either once or twice daily, following dose escalation from 5 to 30µg in Japanese and Caucasian T2DM patients not adequately controlled with sulfonylurea or sulfonylurea and metformin.

The primary objective was to assess the maximum tolerated dose and to assess plasma glucose concentration in response to a standardised breakfast test meal at the highest tolerated dose of lixisenatide in T2DM patients. This has been discussed in the pk section. This section will discuss efficacy only which is AUC (0:29h- 4.30h) PPG.

Standard inclusion (and exclusion criteria) applied.

Table 19: Planned patient assignment

	Japanese	Caucasian		Japanese	Caucasian
	AVE0010	**AVE0010**		**AVE0010**	**AVE0010**
5µg single dose and starting dose for dose escalation			***10µg single dose and starting dose for dose escalation***		
QD	5	5	QD	15	15
BID	5	5	BID	15	15
Placebo	5	5	Placebo	15	15

Table 20: Patient disposition

	Japanese			Caucasian		
		AVE0010			**AVE0010**	
	Placebo	**QD**	**BID**	**Placebo**	**QD**	**BID**
Randomised	21	20	22	19	19	19
Discontinued			1	1		1
Completed	21	20	21	18	19	18

6.2.3. Results

Primary efficacy variable: Pairwise adjusted LS mean differences vs. placebo for the change from baseline in $AUC_{[0:29h-4:30h]}$ of PPG after a standardised breakfast on the last day of the highest well tolerated dose were -333.4 and -288.8 h*mg/dL with lixisenatide QD and BID (all patients), respectively. This was statistically significant (p-value <.0001) in comparison with placebo. For Japanese patients, pairwise adjusted mean differences vs. placebo were -406.7 and -346.3 h*mg/dL and for Caucasian patients -260.1 and -231.3 h*mg/dL in the lixisenatide QD and BID groups, respectively. These differences in comparison with placebo were statistically significant (p-value <.0001) in both lixisenatide QD and BID groups for each ethnicity.

This study is of limited significance as the primary endpoint is not of importance; the numbers in each group are too small to yield meaningful results.

6.3. Add on to basal insulin +/- metformin or sulfonylurea

Two studies are submitted. (EFC 6016 is pivotal and EFC10887 is considered supportive by the evaluator as it was conducted in Asia and only included Asian subjects; thus the relevance to the wider T2DM subjects is uncertain).

6.3.1. Study EFC6016

6.3.1.1. Design

This was a randomised, double-blind, placebo-controlled, 2-arm, unbalanced design, parallel-group, multicentre, multinational 24-week study followed by an extension assessing the efficacy and safety of lixisenatide in patients with T2DM not adequately controlled by a stable dose of

basal insulin with or without metformin. The extension period ended for all patients when approximately 300 patients had been treated for at least 12 months and was stopped for all patients at week 76 of the last randomised patient.[14]

Objectives: Primary*:* To assess the efficacy of lixisenatide on glycaemic control in comparison to placebo as an add-on treatment to basal insulin in patients with T2DM treated with basal insulin in terms of absolute HbA_{1c} reduction over a period of 24 weeks. Thus, the change from baseline inHbA1c was the primary efficacy endpoint.

Secondary: To assess: the effects of lixisenatide on body weight, 2-hour PPG after standardised meal challenge test, percentage of patients reaching HbA1c < 7% and ≤ 6.5%;

FPG; change in 7-point self-monitored plasma glucose (SMPG) profiles and basal insulin and total insulin doses; lixisenatide safety, tolerability and pk; anti-lixisenatide Ab development.

Main inclusion criteria: Patients with T2DM diagnosed at least 1 year before the screening visit; insufficiently controlled with basal insulin at a stable dose (±20%) of at least 30 U/day for at least 2 months prior to screening; and HbA1c ≥ 7% and ≤ 10% at screening. Exclusion criteria were broadly similar to previous studies.

Study treatments: Lixisenatide treatment was as per previous studies.

Patients received insulin for at least 3 months prior to screening with a stable dose (±20%) of ≥ 30 U/day for at least 2 months before screening and throughout the study. At randomisation the insulin dose was reduced by 20% if the screening HbA_{1c} was ≤ 7.5% to lessen the risk of hypoglycaemia. Between Weeks 4 and 12, in the absence of hypoglycaemia, the dose was increased to the screening visit dose. During the study the insulin dose was to remain relatively stable, not exceeding ±20% of the screening dose. A reduction in insulin was considered and initiated, as appropriate, if a patient had hypoglycaemic episodes. For patients on metformin at screening, a stable dose of at least 1.5 g/day was to be maintained throughout the study.

Sample size: This was designed as a superiority study. 300 patients in the lixisenatide treatment and 150 in the placebo treatment arms provided a power of 96 % (or 86 %) to detect differences of 0.5 % (or 0.4 %) in the absolute change from baseline to week 24 in HbA1c between lixisenatide and placebo, assuming the common standard deviation is 1.3 % with a 2-sided test at the 5 % significance level.

Participant flow: 496 patients were randomised with 329 and 167 patients in the lixisenatide and placebo treatment groups, respectively. Of the 496 randomised patients, 495 patients were exposed to the study treatment. Information on patient disposition is presented in the dossier.

Table 21: CSR EFC6016: Analysis populations - Randomised population

	Placebo	Lixisenatide
Randomized population	167 (100%)	329 (100%)
Efficacy population		
Modified Intent-to-Treat (mITT)	166 (99.4%)	327 (99.4%)
Safety population	167	328
PK Population	164	318
PK = pharmacokinetics		

[14] Sponsor clarification, provided in the response to the CER: Further to a study protocol amendment the patient completion date was changed. This sentence should read as follows: "The extension phase ended for all patients at week 76 visit of the last randomised patient"

6.3.1.2. Results

The mean duration (sd) of diabetes was 12.46 years (6.8).The median duration of basal insulin treatment for the study population was 1.75 years. Most patients took either long-acting insulin analogues (glargine [50.1%] and detemir [8.7%]) or NPH (40.0%) at screening, with a few exceptions who were taking premixed insulin. 79.6% of patients in the lixisenatide group and 78.4% with placebo were on metformin at screening with a median duration of 5.74 and 4.84 years respectively and a median dose of 2000 mg/day in both groups.

Treatment compliance was good with 316 patients (96.3%) in the lixisenatide-treated group and 163 (97.6%) in the placebo-treated group having a compliance of 80 - 100%.

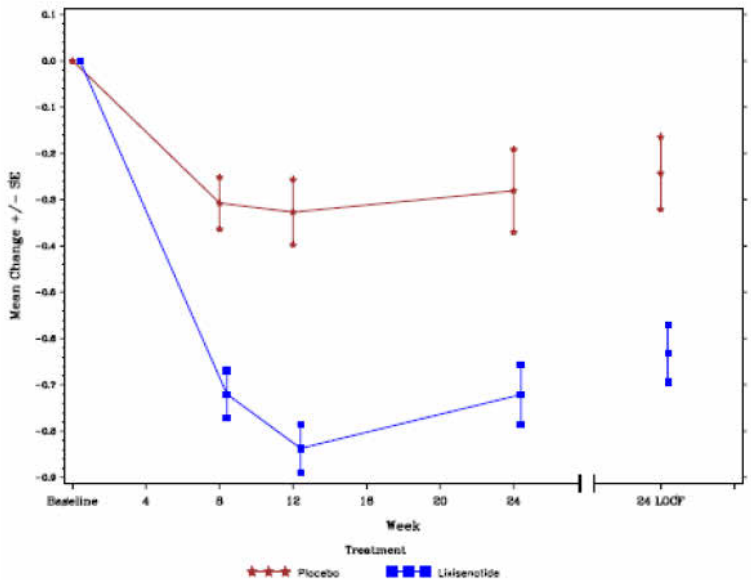
The mean age of the study subjects randomised was 57.2 (9.6) years. Males 46.1 %; Caucasians 77.6%; mean HbA_{1c} 8.48 (0.82). ≥8% was 69.9% and BMI was 32.13 kg/m^2 (6.22).

Primary efficacy variable*:* As shown below the LS mean change from baseline to Week 24 in HbA_{1c} was greater with lixisenatide than placebo (-0.74% and -0.38%, respectively). The LS mean difference for lixisenatide versus placebo was statistically significant, -0.36% (95% CI: -0.550, -0.174; p = 0.0002).

Table 22: Mean change in HbA1c (%) from baseline to Week 24 - mITT population

HbA1c (%)	Placebo (N=166)	Lixisenatide (N=327)
Change from baseline to week 24 (LOCF)		
Number	158	304
Mean (SD)	-0.24 (0.98)	-0.63 (1.08)
Median	-0.30	-0.60
Min : Max	-2.7 : 2.7	-3.5 : 5.7
LS Mean (SE) [a]	-0.38 (0.107)	-0.74 (0.090)
LS Mean difference (SE) vs. placebo [a]	-	-0.36 (0.096)
95% CI	-	(-0.550 to -0.174)
p-value	-	0.0002

Figure 6: Plot of mean change in HbA1c (%) from baseline by visit up to week 24 - mITT population



This shows that the maximum effect was at 12 weeks with increased lessening of effect until the end of the study at 24 weeks. However, at 24 weeks, the mean decrease in HbA_{1c} was around

0.4%.greater with lixisenatide that with placebo. The pattern of lessening effect was seen into the extension period.

Secondary efficacy variables showed similar trends. Of note, a greater LS mean decrease in daily basal insulin dose from baseline to week 24 was reported in the lixisenatide treatment group (-5.62U) compared with placebo treatment group (-1.93 U) and the LS mean difference between the 2 treatment groups (lixisenatide vs placebo) was -3.68 U (95% CI; -6.568, -0.815).

Data are also provided showing that the analysis of the mean change in HbA1c by baseline factors (age, BMI, baseline HbA_{1c} and race) to week 24 did not reveal any notable findings. A sensitivity analysis to assess the impact of rescue medication on mean change in HbA1c reduction supported the primary analysis. It is noted that 80% of the subjects had metformin at baseline. The LS change vs placebo in those who had metformin (n=249) in the lixisenatide group was -0.28 (-0.48 to -0.07); the change in those without metformin (n=55) was -.70 (-1.123 to -0.27). The latter number is those on insulin alone.

Data showing the mean change in HbA1c (%) from baseline to week 24 by anti-lixisenatide Ab status and concentration prior to rescue and/or at week 24 are presented below.

Table 23: Mean change in HbA1c (%) from baseline to Week 24 by anti-lixisenatide antibody status and concentration prior to rescue and/or at Week 24 - mITT population

	Lixisenatide (N=327)			
	N	Mean (SD)	LSMean* (SE)	95% C.I.*
Anti-Lixisenatide antibody status prior to rescue and/or at Week 24				
Positive	170	-0.64 (1.01)	-0.76 (0.108)	(-0.970 to -0.547)
Negative	64	-0.81 (1.11)	-0.95 (0.148)	(-1.236 to -0.656)
Anti-Lixisenatide antibody concentration (nmol/L) prior to rescue and/or at Week 24				
<LLOQ	98	-0.78 (0.93)	-0.87 (0.133)	(-1.131 to -0.606)
1st quartile	11	-0.40 (0.61)	-0.81 (0.298)	(-1.396 to -0.218)
2nd quartile	13	-0.72 (1.09)	-0.77 (0.273)	(-1.311 to -0.233)
3rd quartile	11	-0.80 (0.87)	-0.97 (0.293)	(-1.550 to -0.392)
4th quartile	11	-0.02 (0.85)	-0.32 (0.293)	(-0.901 to 0.261)

A similar pattern was seen for change in HbA_{1C} by Ab status to week 76.

The numbers of patients in the mITT population (lixisenatide 327, placebo 166) are not consistent with the numbers in the analysis of the primary efficacy variable (lixisenatide 304, placebo 158). It is indicated that results from the mITT are used in this analysis.

Also, only 234 patients who received lixisenatide are included in analysis of the efficacy variable by Ab status. Of these, 170 were Ab+ve. However, the data only presents information on Ab concentration for 144 patients. In the safety results, Ab status by visit is provided showing that 248 patients had an Ab measurement at week 24. These data also show that 76.6% of the 94 patients requiring rescue therapy were Ab+ve prior to rescue. The concentration data suggest that patients with higher levels of Abs had smaller decreases in HbA1c.

It is noted that there was a lessening of effect after 24 weeks that continued into the extension period although the difference between mean change in HbA1c with lixisenatide and placebo at the end of 24 weeks and end of treatment was the same at around 0.4%.In addition, 30% of patients with lixisenatide and 40% with placebo required rescue therapy during the whole treatment period. This suggests that lixisenatide may provide some short term insulin sparing.

6.3.2. Study EFC10887

6.3.2.1. Design

This was a randomised, double-blind, placebo-controlled, 2-arm parallel-group, multicentre study with a 24-week treatment period assessing the efficacy and safety of lixisenatide in patients with T2DM insufficiently controlled with basal insulin with or without sulfonylurea.

The **primary and secondary objectives** were similar to the previous study, EFC 6016.

This was conducted at 57 centres in Japan, South Korea, Philippines and Taiwan from March 2009 to June 2010.

The **inclusion criteria** were similar to EFC 6016. Treatment with a stable basal insulin regimen for at least 3 months and at a stable (± 20 %) dose of at least 10 U/day for at least 2 months prior to screening; in those with sulfonylurea treatment, a stable sulfonylurea regimen for at least 3 months prior to screening.

Study treatments: Treatment details were broadly similar to EFC 6016.

Randomisation and blinding methods, statistical methods and analysis populations**:** The randomisation was stratified by screening values of HbA1c (< 8.0%, ≥ 8.0%) and use of sulfonylurea.

Sample size and other statistical considerations were also similar to the previous study.

Baseline data: Data are provided showing that the demographic and patient characteristics at screening or baseline were generally similar between the lixisenatide and the placebo groups for the safety population.

The mean duration of diabetes (years) was 13.92 in both groups. The mean age was 58.4 (10.2) years. The mean duration of diabetes was 13.92; baseline HbA_{1c} was 8.17 (0.85). Those with ≥ 8% was 50.6%.

The mean duration of the treatment with basal insulin at screening was 2.97 years with lixisenatide and 3.01 years with placebo. The mean daily dose of basal insulin was 24.85 U with lixisenatide and 24.11 U with placebo. 95 (61.7%) patients with lixisenatide and 92 (58.6%) with placebo were treated with insulin glargine and 41 (26.6%) with lixisenatide and 42 (26.8%) with placebo were treated with Detemir. 58.4% with lixisenatide and 52.9% with placebo group had a morning injection. 108 (70.1%) patients with lixisenatide and 111 (70.7%) with placebo group, were receiving sulfonylurea as well as basal insulin at screening for a mean duration of 6.07 and 6.80 years respectively. The most frequently used sulfonylurea was glimepiride in 90 (83.3%) with lixisenatide and 81 (73%) with placebo with 56 (51.9%) and 45 (40.5%) receiving doses ≥ 3mg/day respectively.

6.3.2.2. Results

Treatment compliance was (94.2%) in the lixisenatide group and (97.5%) in the placebo group having compliance between 80 - 00%.

Primary efficacy variable*:* 8 patients with lixisenatide and 3 with placebo were excluded from the efficacy analysis due to lack of HbA1C data. Results for the primary efficacy variable are presented below.

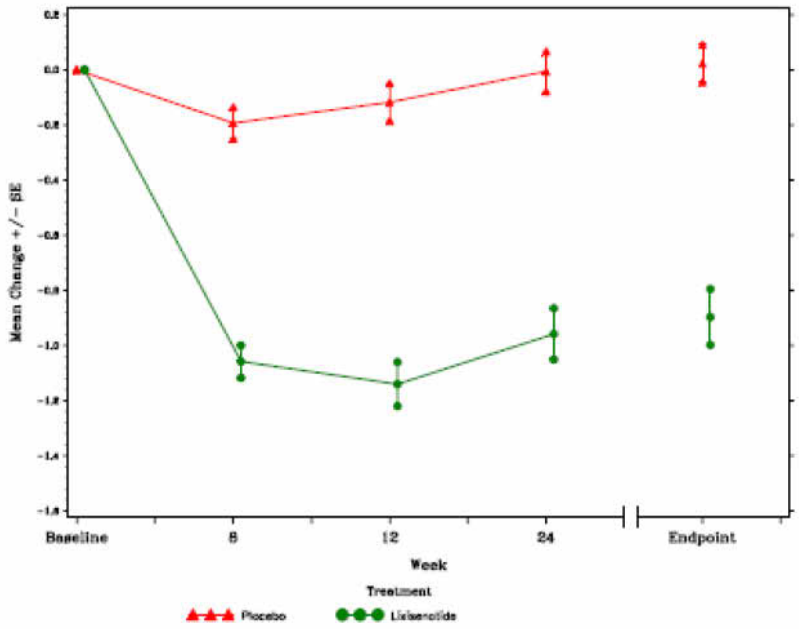
Table 24: Mean change in HbA1c (%) from baseline to endpoint - mITT population

HbA_{1c} (%)	Placebo (N=157)	Lixisenatide (N=154)
Change from baseline to endpoint		
Number	154	146
Mean (SD)	0.02 (0.85)	-0.90 (1.22)
Median	0.00	-0.90
Min : Max	-2.5 : 2.5	-3.3 : 5.7
LSMean (SE) [a]	0.11 (0.131)	-0.77 (0.137)
LSMean difference (SE) vs Placebo [a]	-	-0.88 (0.118)
95% CI	-	(-1.116 to -0.650)
p-value	-	<0.0001

This shows that treatment with lixisenatide resulted in a statistically significant decrease in HbA1c from baseline to week 24 compared with placebo (LS mean change in HbA1c from baseline to week 24, -0.77% with lixisenatide and 0.11% with placebo, with an LS mean difference = -0.88%; 95%CI = -1.116 to -0.650; p-value <0.0001).

A plot of the mean change in HbA1c by visit is presented below. This shows that with lixisenatide HbA1c was already decreased at Week 8 and remained reduced until the end of the treatment period compared with placebo in which no relevant changes of HbA1c were observed.

Figure 7: Plot of mean change in HbA1c (%) from baseline by visit and at endpoint – mITT population



A sensitivity analysis to assess the impact of the rescue therapy on the mean change in HbA1c from baseline to week 24 supported the main analysis.

Key information from results of mean decrease in HbA1c from baseline to week 24 in analyses by baseline characteristics and factors are provided in the dossier. It is noted that 70% had sulfonylurea at baseline. Those having sulfonylurea and those who did not had similar changes in relation to HbA_{1c}.

Results of HbA_{1C} decrease by Ab status are presented below. It is indicated that results for the primary efficacy variable by anti- lixisenatide Ab status showed no relevant differences in the mean change in HbA1c from baseline between Ab+ve and -ve patients. It is noted that the concentration of Ab had no influence on the mean change in HbA_{1c} from baseline in the lixisenatide group taking into account this analysis is limited by very low number of patients in each Ab concentration quartile category.

Table 25: Mean change in HbA1c (%) from baseline to endpoint by anti-lixisenatide Ab status and concentration prior to rescue and/or at the end of treatment - mITT population

	Lixisenatide (N=154)			
	N	Mean (SD)	LSMean (SE)[a]	95% C.I.[a]
Anti-Lixisenatide antibody status prior to rescue and/or at the and of treatment				
Positive	105	-0.91 (1.19)	-0.82 (0.147)	(-1.113 to -0.536)
Negative	34	-0.79 (1.23)	-0.63 (0.208)	(-1.043 to -0.225)
Anti-Lixisenatide antibody concentration prior to rescue and/or at the and of treatment				
<LLOQ	73	-0.89 (1.31)	-0.77 (0.278)	(-1.323 to -0.220)
1st quartile	5	-1.82 (0.84)	-1.55 (0.566)	(-2.670 to -0.422)
2nd quartile	4	-1.45 (0.87)		
3rd quartile	4	0.00 (0.57)		
4th quartile	4	-0.20 (0.32)		

Secondary efficacy analyses: These generally reflected the findings in relation to the primary efficacy endpoint. However, body weight change was not statistically significant compared to placebo.

There are fewer patients in the efficacy analysis by Ab status than in the mITT population. There were 139 patients (105 +ve and 39 –ve) in the mITT analysis whereas the data on Ab concentration only includes 90 patients. Also, there are inconsistencies in the anti lixisenatide Ab data in different parts of the CSR. The pk data described in the body of the CSR states 120 patients were Ab+ve at week 24. Data presented below shows 111 patients Ab+ve at week 24.

Table 26: Number (%) of patients with anti-lixisenatide Ab status by visit during on-treatment period - Safety population

Visit	Antibody Status, n/N1(%)	Lixisenatide (N=154)
Baseline	Positive	5/153 (3.3%)
	Negative	148/153 (96.7%)
Week 2	Positive	8/153 (5.2%)
	Negative	145/153 (94.8%)
Week 4	Positive	43/147 (29.3%)
	Negative	104/147 (70.7%)
Week 24	Positive	110/141 (78.0%)
	Negative	31/141 (22.0%)
Prior to rescue	Positive	1/2 (50.0%)
	Negative	1/2 (50.0%)
Last on-treatment value	Positive	111/153 (72.5%)
	Negative	42/153 (27.5%)

No information is provided on the method for calculation of basal and total insulin doses. Data provided on the daily basal insulin dose and total insulin dose are the same.[15]

The population studied is entirely from Asia (Philippines, Japan, Korea and Taiwan). It does not directly compare with other ethnic groups. In addition, this does not reflect the population that would receive basal insulin in Australia as metformin would the drug of first choice before insulin is added.

6.4. Monotherapy

This is not a requested indication. However these studies provide information on the absolute efficacy and safety magnitudes of lixisenatide, as they are placebo controlled studies. They will be discussed briefly, from that point of view.

6.4.1. Study EFC6018

6.4.1.1. Design

This was a randomised, double-blind, placebo-controlled, 4-arm, unbalanced design, parallel-group, multi-centre, multinational 12-week study assessing the safety and efficacy of lixisenatide in patients with T2DM not treated with anti diabetic agents.

The **primary and secondary efficacy endpoints** are similar to those of the previous studies.

These were treatment naive subjects; other inclusion and exclusion criteria were broadly similar to previous studies.[16]

The subjects were commenced on a 10 µg dose and then titrated up to the 20 µg maintenance dose. **Randomisation** was stratified by screening HbA_{1c} (< 8.0, ≥ 8.0%) and BMI (< 30 kg/m^2, ≥ 30 kg/m^2). Sample size calculations and statistical considerations were similar to previous studies.

[15] Sponsor clarification, provided in the response to the CER: "In study EFC10887, only basal insulin was allowed as background therapy, short-acting insulin was only allowed as a rescue therapy. The efficacy endpoints (including basal and total insulin doses) were analyzed using the mITT population, excluding values obtained after introduction of the rescue therapy. This explains why the 2 analyses provided the same information."

[16] Sponsor comment provided in the response to the CER: "Patients included in Study EFC6018 were patients not currently treated with antidiabetes agents. Not all patients included were treatment naive. This sentence should be: "These were treatment naive subjects not treated with antidiabetes agents for at least 3 months at screening; other inclusion and exclusion criteria were broadly similar to previous studies."

Participant flow: 361 patients were randomised, 61 each in the placebo 2- and 1-step titration arms, and, 120 in lixisenatide 2-step and 119 in lixisenatide 1-step titration arms. 30 patients prematurely discontinued from study treatment. The percentages that discontinued were similar with placebo and lixisenatide (7.4% and 8.8%, respectively). There was no difference in the percentages of patients who discontinued between the lixisenatide titration arms. The main reason for discontinuation was "other" followed by AEs. Information on patient disposition is presented below.

Data are provided showing that the **demographic and baseline characteristics** at screening were generally similar across all treatment groups for the safety population. Of note, the median baseline HbA_{1c} in the combined placebo and lixisenatide groups was 8.0%. Also, across all treatment groups, only 5 patients had prior use of an antidiabetic medication.

6.4.1.2. Results

Treatment compliance (95.8%) in the combined lixisenatide and (99.2%) in the combined placebo groups had a compliance of 80 - 100%.

Primary efficacy variable*:* As shown below, there was a statistically significant decrease in HbA1c from baseline to week 12 in those receiving lixisenatide compared to placebo.

Table 27: Mean change in HbA1c (%) from baseline to endpoint – mITT population

		Lixisenatide	
HbA1c (%)	Placebo Combined (N=121)	Two-step Titration (N=120)	One-step Titration (N=118)
Change from baseline to endpoint			
Number	112	113	114
Mean (SD)	-0.27 (1.09)	-0.77 (0.94)	-0.94 (0.72)
Median	-0.30	-0.80	-0.90
Min : Max	-2.7 : 3.3	-3.0 : 3.1	-3.0 : 0.8
LS Mean (SE) [a]	-0.19 (0.121)	-0.73 (0.116)	-0.85 (0.119)
LS Mean difference (SE) vs. placebo combined [a]		-0.54 (0.123)	-0.66 (0.122)
95% CI		(-0.785 to -0.300)	(-0.903 to -0.423)
p-value		<0.0001	<0.0001

Data are provided showing that: a sensitivity analysis to assess the impact of rescue medication supported the main analysis; subgroup analysis by country and baseline factors such as race, gender, ethnicity, age group, and baseline BMI and HbA1c showed that the efficacy of lixisenatide was similar.

It is indicated that there were no relevant differences between Ab+ve and -ve patients in the mean change in HbA1c from baseline to week 12 as shown below.

It is noted that with lixisenatide 1-step titration, the mean reduction in HbA1c seemed to be smaller with the increase in Ab concentration whereas this did not appear to be the case with lixisenatide 2-step titration. It is considered that the results of the analysis are limited as there were small numbers in each concentration quartile.

Table 28: Mean change in HbA1c (%) from baseline to endpoint by anti-lixisenatide Ab status prior to rescue and/or at the end of treatment – mITT population

	Lixisenatide							
	Two-step Titration (N=120)				One-step Titration (N=118)			
	N	Mean (SD)	LSMean (SE)[a]	95% C.I.[a]	N	Mean (SD)	LSMean (SE)[a]	95% C.I.[a]
Anti-Lixisenatide antibody status prior to rescue and/or at the and of treatment								
Positive	46	-0.98 (0.75)	-0.93 (0.149)	(-1.219 to -0.633)	52	-0.98 (0.73)	-0.82 (0.151)	(-1.120 to -0.527)
Negative	38	-0.79 (0.97)	-0.69 (0.169)	(-1.026 to -0.361)	34	-0.93 (0.78)	-0.88 (0.172)	(-1.216 to -0.539)
Anti-Lixisenatide antibody concentration prior to rescue and/or at the and of treatment								
<LLOQ	10	-1.17 (0.49)	-1.06 (0.244)	(-1.548 to -0.574)	25	-0.97 (0.72)	-0.93 (0.155)	(-1.235 to -0.617)
1st quartile	6	-0.57 (1.13)	-0.51 (0.313)	(-1.138 to 0.113)	7	-1.24 (0.70)	-1.00 (0.313)	(-1.630 to -0.379)
2nd quartile	7	-1.24 (0.91)	-1.34 (0.292)	(-1.920 to -0.754)	7	-0.59 (0.65)	-0.71 (0.287)	(-1.286 to -0.142)
3rd quartile	10	-0.58 (0.46)	-0.96 (0.244)	(-1.445 to -0.469)	4	-0.85 (0.70)		
4th quartile	8	-0.89 (0.96)	-0.96 (0.274)	(-1.510 to -0.416)	5	-0.26 (0.48)	-0.35 (0.352)	(-1.048 to 0.357)

This provides evidence of absolute efficacy in the treatment naive subjects: mean change in HbA_{1c} of 0.66% to 0.50% over placebo in 13 weeks.

6.4.2. Study LTS10888

6.4.2.1. Design

This was a randomised, open label, parallel-group (1- and 2-step titration), multicentre single country (Japan) 52-week study followed by a 24-week extension assessing the safety and tolerability of lixisenatide monotherapy in patients with T2DM.

69 patients were randomised, 36 in the 1-step titration group and 33 in the 2-step titration group. All were exposed to study treatment. Information on patient disposition is provided in the dossier.

Baseline data: Data are provided showing that the demographic and patient baseline characteristics were generally similar between the 2 titration groups for the safety population. Around 50% were on an oral antidiabetic medication at screening with most on a sulfonylurea.

6.4.2.2. Results

At week 24, the mean (SD) change from baseline in HbA1c (%) was -0.99 (1.07) and -0.74 (0.79) for the 2-step and 1-step titration groups, respectively. In the pooled titration group, the mean (SD) change from baseline was -0.83 (0.96) at week 52 and -0.72 (1.20) at week 76. The corresponding results using LOCF were -0.44 (1.17) at week 52 and -0.32 (1.23) at week 76 (last value on-treatment). The mean change from baseline in HbA1c over time at weeks 24, 52 and 76 showed that the HbA1c reduction was maintained until about week 66.

6.5. Evaluator's overall conclusions on efficacy

The following are relevant.

- Site of administration

It is stated in the study protocols that, "the investigation product should be administered by deep subcutaneous injection, alternating between the left and right anterolateral and left and right posterolateral abdominal wall, thighs and upper arm. Within a given area, location should be changed (rotated) at each time to prevent injection site skin reaction". The draft PI is lacking in detail in relation to this. The above mentioned directions should be included in the PI.

· Absolute efficacy vs placebo

In a double blind randomised 13 week study (EFC 6018) in treatment naive subjects[17], the absolute efficacy was modest in relation to HbA_{1c}: the LS mean difference vs placebo was -0. 54% (0.123) and - 0.66% (0.122) in the two and one step titration of lixisenatide groups respectively.

· Dose selection for the pivotal studies

There is one placebo controlled randomised study, DRI6012 where groups of approximately 50 T2DM patients were administered once daily or twice daily 5, 10, 20 or 30 µg/ day for 13 weeks, that suggests that the optimum maintenance dose is 20 µg. This was seen in relation to the primary efficacy parameter HbA_{1c}.

· Racial mix of the recruited subjects

Most of the efficacy studies had a preponderance of Caucasians except Study EFC 6015 (44.8% Asian) and EFC 10887 (mostly Asian). Study EFC 6015 which had a reasonable mix of Asians showed that the LS mean change in HbA1c from baseline to week 24 was greater in Asians than Caucasians (-0.93 and -0.61% respectively).[18] Thus, these studies do not reflect adequately the target population in Australia. In the presentation of study findings in the CLINICAL TRIALS section, the percentage of Caucasians and other racial groups should be specified.

· Antibodies and their influence on efficacy

A meta-analysis of change in HbA_{1c} from baseline to week 24 by anti-lixisenatide Ab status and measured antibody concentrations using combined data from EFC6015, EFC6016, EFC10743, and EFC10887 was presented. This included 998 patients of whom 693 (69.4%) were Ab+ve. Ab concentration was measured in 681of whom 550 had been assessed as Ab+ve with Ab status not available in the remaining 131. The Ab concentration was <LLOQ (3.21 nmol/L) in 477/681 (70.0%) patients.

There are discrepancies in the numbers of patients with Ab measurement with 998 and 986 noted in separate paragraphs of describing this analysis. Although this is a small difference, it suggests lack of clarity around Ab measurements. Also, it is concerning that samples were not adequate to measure Ab when this was a stated study objective.

Data from placebo controlled studies with an extension show there was an increase in the numbers of patients requiring rescue therapy over the entire treatment period compared with the 24 week period. In those receiving lixisenatide, there was a high proportion were Ab+ve prior to rescue. These data are tabulated below.

[17] Sponsor clarification, provided in the response to the CER: Study EFC6018 was a 12 week study in treatment subjects not treated with antidiabetes agents for at least 3 months at screening.
[18] Sponsor clarification, provided in the response to the CER: "Most of the efficacy studies had a preponderance of Caucasians except Study EFC6015 (44.8% Asian) and EFC10887 (all Asian). Study EFC6015 which had a reasonable mix of Asians showed that the LS mean change in HbAlc from baseline to week 24 was -0.95% in Asians and -0.78% in Caucasians."

Table 29: Percentage of patients requiring rescue therapy and antibody status at the time of rescue

	Lixisenatide*				Ab+ve prior to rescue	Placebo*
	Morning		Evening			
ECF6015						
24 week period	4.0		-			12.6
Entire period	27.0		-		104/148 (70.3%)	38.8
EFC6016						
24 week period	5.8		-			7.2
Entire period	29.7		-		72/94 (76.6%)	41.6
ECF10743						
	A	B	A	B		
24 week period	3.1	1.3	-	-		4.4
Entire period	18.8	22.8	-	-	28/36 (77.8%)	38.4

*percentages of patients requiring rescue therapy
Study ECF10743: A = 2 step titration; B = 1-step titration
Ab+ve data: the number and percentage of patients receiving lixisenatide requiring rescue who were Ab+ve prior to rescue

It is recognised that these data are difficult to interpret as not all patients had Ab status assessed. Notwithstanding this, the results suggest that the presence of Ab may be associated with decreased efficacy. The sponsor notes that the increased requirement for rescue therapy is consistent with the patient population and progression of T2DM. However, decreased efficacy due to immunogenicity is referenced in the proposed PI.

· Body weight changes

The reduction predictably varied in the studies. The mean change over placebo in the 'add on metformin' studies was -2.10 to 2.63 kg. In the exenatide comparator study, the change was -2.98 vs 3.98 kg (lixisenatide vs exenatide). The 'add on to insulin' studies, the values were -0.84 to -1.28. These were changes reported at 24 weeks and no study tested these changes independent of nausea and vomiting.

· Add on to metformin

There were 2 placebo controlled double blind studies of 24 weeks[19] (EFC 6014 and EFC 10743). These studies included sufficient number in each study arm to show superiority of lixisenatide over placebo. The absolute margin of difference in HbA_{1c} was 0.4% that was factored into the statistical testing to show superiority and this margin is generally acceptable.

The subjects were T2DM subjects who were on maximum dose of metformin (1500 mg/day). Their mean HbA_{1c} was approximately 8.16% also suggests that they were suitable for the addition of another antidiabetic agent (in this case, lixisenatide). They were significantly overweight with the mean BMI being over 32 and 33 kg/m^2. The population tended to be Caucasians in over 85% and does not reflect the other ethnic groups adequately.

The LS mean difference over placebo was approximately 0.41% to 0.48 % in relation to mean change from baseline of HbA_{1c}. Thus, predefined superiority was seen, though the magnitude is modest. The secondary endpoints showed similar trends. The change in HbA_{1c} appeared to be maintained over 76 weeks.

There was a reduction of -2.0 to -2.6 kg in body weight over the 24 weeks in the lixisenatide group. The change over placebo was not clinically significant. This endpoint is not independent of nausea and vomiting.

There was one active comparator study, **EFC 6019** which used exenatide as the comparator at the dose that it is registered in Australia, which provides useful information. This was designed as a non-inferiority study and non-inferiority was demonstrated if the upper bound of the 2 sided 95%CI of the LS mean difference was less than of 0.4%. This is wider than it should have been as the placebo controlled superiority studies only included a margin of 0.4 to 0.5%. This is reinforced in the EMA Guideline CPMP/EWP/1080/00/Rev 1, where it is recommended that for a non-inferiority study, a margin of 0.3 % is generally acceptable. The sponsor should justify the wider margin used in this study.[20]

These subjects also had a baseline HbA_{1c} of 8.03 % with a median duration of metformin of 2.49 years with maximum dose (≥ 1500mg/day) suggesting that the population was a suitable target population for add on therapy. Again the recruitment of 92.7% Caucasians does not reflect the T2DM population in Australia. Though this study showed non-inferiority in terms of the primary endpoint and efficacy endpoints relating to HbA_{1c}, exenatide fared better. This was also seen in relation to body weight loss. The draft PI should include the details of the non-inferiority margins in the study description. It should also have details of the study design, subject number and the primary efficacy endpoint and statistical testings included.

Analysis of efficacy by antibody status was provided in Study **EFC 10743** in the m ITT population, where the mean change from baseline in Hb A_{1c} was lower -0.76 % (0.83) in the antibody positive group in the one step titration group vs -1.11% (0.99) in those without antibodies. This was also seen in those with the 2 step group. This was the results presented at 76 weeks.

[19] Sponsor clarification provided in the response to the CER: "There were 2 placebo controlled double blind studies with a **main treatment period** of 24 weeks (EFC6014 and EFC 10743).

[20] A justification was contained in the sponsor's response to the CER, which the following introductory paragraph: "The Phase 3 clinical development plan of lixisenatide, including Study EFC6019, was designed in 2007 based on relevant guidelines in force at this time, and studies were initiated in 2008. In accordance with EU, Study EFC6019 was an active-controlled study evaluating safety and efficacy of lixisenatide as compared to exenatide. Exenatide was selected as a relevant comparator since it belongs to the same class of GLP-1 receptor agonist, and was the only compound in this class approved at the time of study initiation (marketing authorisation application granted in November 2006 in the EU)….."

This is a concern. These findings should be included in the PI. The sponsor should state how it proposes to monitor for lack of efficacy in patients administered lixisenatide over a prolonged period.[21]

· Add on to sulfonylurea

As dual therapy, data are provided only in one good quality (randomised double blind placebo controlled study) Phase 3 study, EFC 6015, in a subgroup, only. This study included those on sulfonylurea with or without metformin. Those having sulfonylurea with lixisenatide included only 16% of those randomised, placebo (n=45, 15.8%) and lixisenatide (n=91, 15.9%). Analysis of efficacy in this subgroup was factored in the prestudy considerations. Statistically significant efficacy over placebo was seen in this subgroup (-0.85; 95% CI: -1.161, -0.543). Other data to support dual therapy was in PDY 6797 which was too small to yield conclusive findings.

The efficacy data are not clinically significant as the numbers are too small. Further data are required to support use with sulfonylurea as dual therapy.

· As triple therapy with sulfonylurea and metformin

The pivotal study was **EFC 6015**.This was double blind randomised placebo controlled study of T2DM subjects where 84% metformin and sulfonylurea at baseline. The mean HbA_{1c} at baseline was 8.36%; the median duration of diabetes mellitus was 8 years. These subjects were on maximum dose of sulfonylurea and metformin. Their baseline BMI was 30.22 kg/m^2 (6.22). This suggests that the target population was suitable for the addition of lixisenatide. This study also had a greater representation of Asians and Orientals (44.8%) and 52% Caucasians.

Overall, efficacy was statistically significant over placebo, and appeared to be maintained over the extension period of 76 weeks, see Figure 5 *Plot of mean change in HbA1c (%) from baseline by visit - mITT population*. These trends were also seen with the secondary efficacy endpoints.

This study also showed that the magnitude of change in HbA_{1c} was less in those with the highest concentration of antibodies. However, this is difficult to interpret due to the small numbers.

· Add on to insulin

There are two studies (EFC 6016 and EFC 10887) which were randomised placebo controlled studies on subjects with stable dose of insulin (≥ 30U) and metformin (≥1.5 g) in study EFC 6016 and sulfonylurea in EFC 10887. Both studies were designed as superiority studies (over placebo) and this was achieved. There are no comparator (non-inferiority studies) with agents that are registered as add on regimen with insulin. The target population in study EFC 6016 reflected the population that would generally require add-on treatment: mean duration of diabetes 12.6 years; on maximum treatment of metformin (2000 mg/day) for a median duration of 5.74 years; 20 % had only insulin in Study EFC 6016. The subjects were overweight with a mean BMI of 32.13; mean HbA_{1c} was 8.48 (0.82). This study showed some insulin sparing (secondary efficacy endpoint).

In study EFC 10887, the population was Asian (100%). This study was conducted in Asia and the treatment practices were somewhat different; the target population was those who had insulin added on to sulfonylurea. The mean baseline HbA_{1c} was less than that in the previous study being 8.17%. The mean duration of DM was also longer being 13.92 years. This study is supportive (in terms of reflecting the target population for this proposed indication in Australia). There was statistically significant difference over placebo in relation to the primary efficacy endpoint at 24 weeks as per Study 6016. However the maximal change was seen at 12

[21] In the response to the CER, the sponsor stated: "Usual standard of care recommends the assessment of HbA1c every 3 months in patients with type 2 diabetes (Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes, Diabetes Care, Vol 35, June 2012). This would detect potential lack of efficacy in patients administered over a prolonged period."

weeks and the effect appeared to wane over time (see Figure 6 on *Plot of mean change in HbA1c (%) from baseline by visit up to week 24 - mITT population*).

The use of lixisenatide with insulin alone is based on a subpopulation in these studies. It is 20% in EFC 6016 and 30% in EFC 10887. This number is inadequate to assess efficacy, especially as one of the studies did not reflect the target population in Australia.

Study EFC 6016 also tended to show that the presence of antibodies reduced the magnitude of efficacy in relation to the primary efficacy endpoint. The numbers were inadequate in study 10887 to yield meaningful results.

7. Clinical safety

There were no pivotal studies that assessed safety as a primary outcome. Studies providing evaluable safety data in the dossier are:

- Clinical pharmacology studies in healthy subjects and patients with T2DM
- A study to select dosage in patients with T2DM
- A dosage escalation study in patients with T2DM
- 1 phase 3 safety study
- 7 pivotal and 1 supportive phase 3 efficacy studies

The **safety variables** assessed were**:** treatment emergent adverse events (TEAEs) coded using MedDRA; AEs of special interest hypoglycaemia, allergic or allergic-like reactions, local tolerability, GIT disorder, cardiovascular (CV), serum calcitonin, suspected pancreatitis; laboratory safety parameters; other safety parameters: physical examination, vital signs, body weight, height, and waist measurement and ECG. Serum calcitonin was an AE of interest due to reports of thyroid C-cell proliferation in animal studies with other GLP-1 agonists.

The **safety analysis** was undertaken on the safety population which included all randomised subjects who took at least 1 dose of the study medication. AE data are presented with standard frequency tables. Descriptive statistics, number and percentage of subjects with PCSAs by treatment group and shift tables showing changes with respect to the PCSA between baseline and on-treatment period are presented for the laboratory safety variables. For vital signs, the number and percentage of normal, abnormal and missing findings from the physical examination at baseline and at endpoint are summarised by treatment and shift tables between baseline and endpoint presented. From ECG recordings, heart rate (beat/min), PR (ms), RR (ms), QT interval (ms), QRS (ms), derived QTcB (ms) and QTcF (ms) are summarised by treatment groups at baseline and at endpoint, respectively. The ECG change from baseline to endpoint is summarised by treatment group. The number and percentage of subjects by investigator ECG interpretation (normal, abnormal) are summarised by treatment group. The frequency and percentage of subjects in pre specified QTcB and QTcF interval categories are presented by treatment group.

Independent allergic reaction (ARAC) and CV adjudication committees were established to assess possible events of this type in the safety and efficacy studies.

The dossier also includes an integrated safety analysis (ISA) in the Summary of Clinical Safety. This included an analysis of CV safety. The statistical analysis plan and integrated data used in the ISA were also provided: *Reports of Analyses of Data from More than One Study: ISS*.

7.1. Overview of safety in the clinical pharmacology studies

396 subjects (healthy and T2DM) have been included in the pharmacology studies. There have been single dose and multiple dose (up to 12 week duration) studies.

In these studies, most common TEAEs have been GIT events. There was one withdrawal due to increased CPK (Study BDR 6864), neutropenia n=1 (PDY 11941), urticaria n=2 (TES 6865), rash (PDY 10931).

7.2. Overview of safety in dose selection and safety and efficacy studies

The main dose selection study was DRI6012.

7.2.1. DRI6012: Dose Selection

This was a placebo-controlled, randomised, parallel-group study to evaluate the dose-response relationship of lixisenatide administered once and twice daily with chronic dosing in metformin-treated subjects with T2DM. The study treatments were QD or BID lixisenatide 5, 10, 20 or 30µg or placebo.

The safety population: lixisenatide n= 325[22] subjects vs 109 in placebo group. Mean duration of exposure was 84-89 days. There was no significant difference in the TEAEs between the regimens; however there was dose resposne seen with the TEAEs: total TEAEs ranged from 56% with 5 µg OD to 74.1% with 30 µg bd vs 59.6% placebo. The common events were GIT events which ranged from 21.8% to 57.4%; of which nausea was 7.5% (5 µg OD) to 33.3% with the 30 µg bd. There were 4 subjects (0.93%) who reported allergic events with lixisenatide vs 3 (2.75%) in the placebo group. There was one anaphylactic reaction in the lixisenatide group that was reported as an SAE. Subjects withdrawing due to TEAEs also showed dose response: (1.8% in placebo to 11.1% in the 30 µg QD group and 14.8% in the 20µg BD group). There were no deaths.

7.2.2. Efficacy and Safety Studies

7.2.2.1. EFC6014: Add on to Metformin: Placebo Controlled

The safety population: placebo n= 170 and lixisenatide n = 510 (in those given morning or evening lixisenatide injections). The mean duration (sd) of exposure was 530 (207) days. The percentage of patients experiencing TEAEs were comparable in the lixisenatide treatment groups (84.7% in the morning group) and 83.5% in the evening group; vs 75.3% in the placebo group.

There were three deaths in the lixisenatide group; (the causes were pancreatic cancer, haemothorax and lymphoma). These were deemed not related and this conclusion is acceptable based on the individual patient data provided.

The percentage leading to withdrawal was 8.2 % in the morning group and 9.4% in the evening group vs 3.5% in the placebo group. The common TEAE leading to withdrawal was nausea: 2.4% in the morning group and 2.7% in the evening group vs none in placebo group.

Common TEAEs: Nausea- 25.1% in the morning group and 24.7% in evening group vs 9.4% in placebo group. Vomiting - 13.7 to 15.7% in lixisenatide groups vs 5.3% in placebo.

Symptomatic hypoglycaemia (protocol defined) was 7.1 to 8.6% in the lixisenatide group vs 2.4% in placebo. There no severe symptomatic hypoglycaemia.

Allergic reactions adjudicated as such by the ARAC was reported for 10 patients; 3 (1.2%) in the morning group; 4 (1.6%) in the evening group and 3 (1.8%) in the placebo group. One patient in the lixisenatide morning group was adjudicated as having anaphylactic reaction and angio-

[22] Sponsor correction: n = 433, rather than 325.

edema. Another patient in the pm group had non serious allergic dermatitis; both these patients were withdrawn from the study.

Pancreatic enzymes: 13 patients had elevations (lipase or amylase) 3 (1.2%) in the morning group, 9 (3.5%) in the evening group and 1 (0.6%) in the placebo group. There were no confirmed cases of pancreatitis. However there were 4 reports of withdrawal due to elevated pancreatitis enzymes one of which also had a diagnosis of suspected pancreatitis.

Cardiac disorders (SOC) were reported for 6.7% in the morning group and in 8.2% in the evening group and 2.9% in the placebo group. HLGT was similar between groups being 1.4% in lixisenatide and 1.2% in placebo.

7.2.2.2. EFC10743: Add on to Metformin: Placebo Controlled

Safety population: lixisenatide groups n= 322 subjects vs 160 in the placebo group. The mean duration of exposure was 528.3 days in the active vs 576 days in the placebo group.

Patients with TEAEs were similar between active and placebo groups (approximately 85%).

Nausea was the most frequently reported TEAE in both lixisenatide groups: 38.5% with lixisenatide 2-step titration and 29.2% with lixisenatide 1-step titration; 8.1% placebo-treated patients reported nausea. Vomiting was also frequently reported in lixisenatide-treated patients, 18.0% with lixisenatide 2-step titration and 13.0% with lixisenatide 1-step titration, compared to 1 placebo-treated patient.

Deaths: 6 deaths were reported during the study period; (3 in lixisenatide and 3 in placebo). The deaths in the lixisenatide group were CVA=2 and pancretaic cancer=1).

Withdrawals due to TEAEs were 8.7-11.8% in the lixisenatide groups vs 5.6% in the placebo group. The common reason for withdrawal was nausea (3.7%).

SAEs were experienced in 13.0% patients with lixisenatide 2-step titration, 9.9% with lixisenatide 1-step titration, and 13.8% in the combined placebo group during the total treatment period.

Symptomatic hypoglycaemia as per the protocol definition was reported in 7.5% patients with lixisenatide 2-step titration, 3.7% with lixisenatide 1-step titration, and 7.5% in the combined placebo group.

During the total on-treatment period, injection site reaction AEs were reported in 5.6% patients in each lixisenatide titration group and 1.9% in the combined placebo group.

Allergic reactions: 16 events in 15 patients (6 [3.7%] with lixisenatide 2-step titration, 3 [1.9%] with lixisenatide 1-step titration, and 6 [3.8%] in the combined placebo group) were adjudicated as an allergic reaction. Two of these events (one in each lixisenatide group) were adjudicated as “possibly related to the investigational product” and resulted in withdrawal.

Pancreatitis: During the total on-treatment period 13 patients had changes in pancreatic enzymes, lipase, or amylase reported on the AE form for suspected pancreatitis, 4 (2.5%) patients in each lixisenatide titration group and 5 patients (3.1%) in the combined placebo group. No confirmed cases of pancreatitis were reported during the study.

Calcitonin levels: During the total on-treatment period, 3 patients had a TEAE (levels ≥20 ng/L) of increased serum calcitonin, 1 (0.6%) in each lixisenatide titration group and 1 (0.6%) in the combined placebo group. The events with lixisenatide did not have any associated thyroid disorder and or result in treatment discontinuation.

7.2.2.3. EFC6019: Add on to Metformin: Active comparator, exenatide

The safety population: lixisenatide n= 318 and exenatide n=316. Mean exposure was approximately 480 days.

The percentage of subjects with TEAEs was comparable between groups being 80.8% vs 83.5% respectively. The percentage of nausea was 28.6% with lixisenatide vs 37.7% in exenatide group.

Symptomatic hypoglycaemia as per the protocol definition was reported in 5.0% patients with lixisenatide and 14.6% with exenatide. Those with blood glucose <60 mg/dL was also less with lixisenatide being 4.7% vs 12.0% in exenatide group.

Injection site reactions were reported 9.1% with lixisenatide and 2.2% with exenatide. 3 patients (0.9%) in the lixisenatide treatment group had injection site reactions that led to discontinuation of study treatment.

Allergic events: 1.9% patients and 0.9% with lixisenatide and exenatide respectively were adjudicated as having an allergic reaction.

Pancreatitis: 1.6% with lixisenatide and 2.8% with exenatide, had events of changes in pancreatic enzymes, lipase, or amylase reported on the suspected pancreatitis AE form. Of these, 1 patient receiving exenatide was diagnosed with pancreatitis.

Treatment related withdrawals were similar in both group (14.2%). There were three deaths in each group. In lixisenatide (sepsis, myocardial infarction and metastasis were the cause (s) of death).

Cardiovascular events: Cardiac events (SOC) were 5% in the lixisenatide group and 3.8% in the exenatide group. HLGT featured cardiac arrhythmias (3.8% vs 1.9); coronary artery disease (0.6% vs 0.9%).

Renal function tests*:* The overall incidence of PCSAs for creatinine (≥30% change from baseline) was similar in the 2 groups, 10.9% of patients with lixisenatide and 13.9% with exenatide.

7.2.2.4. EFC10780: Add on to Metformin: Active Comparator, sitagliptin

The safety population: lixisenatide group n=158 and in the sitagliptin group n= 161. The mean duration of treatment was 154 and 160 days respectively.

Patients with TEAEs were similar, 63.9% in the lixisenatide group and 60.9% in the sitagliptin group. There were no deaths reported in this study. Withdrawals due to TEAEs were 2.5% vs 3.1% respectively.

Nausea was the most frequently reported TEAE with lixisenatide (17.7%) compared to (6.8%) patients with sitagliptin. SAEs were reported for 1.9% patients with lixisenatide (which included anaphylactic reaction) and 1.9% with sitagliptin. .During the on-treatment period, the prespecified AE form for suspected pancreatitis was completed for 6 patients (3.8%) with lixisenatide and 2 (1.2%) with sitagliptin. There were no confirmed diagnoses of pancreatitis.

7.2.2.5. EFC6015: Add on to Sulfonylurea +/- Metformin

The safety population was placebo (n=285) vs lixisenatide (n=574). Mean duration of exposure was 530 days in each of the groups. TEAEs were 81.5% in the lixisenatide group vs 75.8% in placebo treated group.

The incidence rate was ≥2% higher with lixisenatide than with placebo for the following TEAEs, respectively: hypoglycaemia (24.6% and 19.3%), nausea (28.0% and 8.8%), vomiting (10.6% and 5.3%), tremor (3.1% and 1.1%), dizziness (10.5% and 6.3%), vertigo (2.4% and 0.4%), gastritis (2.8% and 0.7%), diarrhoea (12.4% and 9.5%), dyspepsia (5.9% and 1.4%), abdominal distension (3.7% and 1.1%), back pain (6.3% and 4.2%), and fatigue (4.4% and 2.1%).

During the total treatment period, SAEs were observed in 10.1% patients with lixisenatide and 12.3% with placebo.

There were 4 deaths, 3 were in the lixisenatide group. Cause of death (myocardial infarction 1, sudden death 1 and multiorgan failure 1). AEs leading to withdrawal: 12.4% with lixisenatide and 7.7% with placebo. The most common reason in both groups was GIT TEAEs, 6.4% and 2.1% with lixisenatide and placebo respectively.

Protocol definition of symptomatic hypoglycaemia: 22.1% with lixisenatide and 17.9% with placebo.

Allergic reaction: 1.9% and 0.4% with lixisenatide and placebo respectively were adjudicated as an allergic reaction, but only 1 event (urticaria-like skin reaction) from a lixisenatide-treated patient was adjudicated as possibly related to study treatment.

Pancreatitis: There were 7 confirmed cases of pancreatitis in 7 patients. Of these, 5 (0.9%) were with lixisenatide (1 pancreatitis, 2 acute pancreatitis, and 2 chronic pancreatitis) and 2 (0.7%) were with placebo (1 acute pancreatitis and 1 responsive pancreatitis).

There were no significant changes relating to serum calcitonin or renal function test.

The population that did not have metformin at baseline (ie the data to support dual therapy with sulfonylurea) included 46 in the placebo and 88 in the lixisenatide group. The range and incidence on TEAEs were similar to the entire groups. However, due to the smaller numbers, it is not conclusive.

7.2.2.6. PDY6797: Add on to Sulfonylurea +/- Metformin

This is a small study comparing pk and safety in Japanese vs Caucasians in small groups (n-20). The results are of limited relevance.

7.2.2.7. EFC6016: Add on to Basal Insulin +/- Metformin

The safety population analyses: placebo n=167; and lixisenatide n=328. The mean (sd) days of exposure are 510 (210) in placebo vs 491 (233) in lixisenatide.

The percentage of TEAEs was similar being 85.6% in the placebo and 87.5% in the lixisenatide group. During the total treatment period, the most commonly reported TEAE in both treatment groups was hypoglycaemia, 42.1% and 40.7% patients with lixisenatide and placebo respectively. This was followed by nausea, 29.3% vs 9.6%; headache, 12.5% vs 10.2%; and diarrhoea, 11.3% vs 6.0% .

The most frequent SAEs were from the infections and infestations lixisenatide: 3.4% vs placebo 1.2% and cardiac disorders SOCs (lixisenatide (1.5%); placebo (5.4%). Treatment-related SAEs were hypoglycaemia, hypoglycaemic unconsciousness, and pancreatic carcinoma with lixisenatide, and myocardial infarction with placebo. One patient with lixisenatide had a SAE of pancreatitis which was assessed as not treatment related however led to treatment discontinuation.

There were 3 deaths in the lixisenatide group (Acute myocardial infarction-1, sudden cardiac death-1and pulmonary TB-1). None of the deaths were assessed as treatment related. Permanent discontinuation of study treatment: 10.7% vs 7.2% in lixisenatide vs placebo respectively. The difference in the percentage between the 2 groups was largely due to the higher frequency of TEAEs leading to treatment discontinuation from the GIT disorders SOC with lixisenatide 5.2% compared with placebo 1.2%.

The percentage of patients with hypoglycaemia TEAEs was similar in the 2 treatment groups, 42.1% patients with lixisenatide and 40.7% with placebo.

Reports from 11 patients, 8 (2.4%) and 3 (1.8%) with lixisenatide and placebo respectively were adjudicated as an allergic reaction.

Seven patients had increases in pancreatic enzymes reported as suspected pancreatitis, 6 (1.8%) patients with lixisenatide and 1 (0.6%) with placebo. One patient receiving lixisenatide had a confirmed diagnosis of pancreatitis and was discontinued from the study. Of the remaining 5 patients receiving lixisenatide, 1 had a severe AE, pancreatic enzymes increased, however this did not led to treatment discontinuation.

Those without the use of metformin were placebo=36 and lixisenatide n=69. The events were similar in those who had metformin and those who did not.

7.2.2.8. EFC10887: Add on to Basal Insulin +/- Metformin or Sulfonylurea

The safety population placebo n=157; lixisenatide n=154. Mean duration of exposure was 154 and 157 in the groups. This study population included Asians only.

The incidence of TEAEs was higher with lixisenatide 89% than placebo 70.1% patients.

The most frequently reported TEAEs were hypoglycaemia, nausea, vomiting and nasopharyngitis. Nausea was reported more frequently with lixisenatide than placebo with 39.6% vs 4.5% respectively. Most were mild in intensity and assessed as treatment related. Events of nausea led to treatment discontinuation in 3.9% with lixisenatide and none with placebo.

Hypoglycaemia was reported in 43.5% patients with lixisenatide and 23.6% with placebo. These met the protocol definition or hypoglycaemia in 42.9% with lixisenatide and 23.6% with placebo.

There were no deaths in the lixisenatide group. SAEs were reported in 6.5% with lixisenatide and 5.7% with placebo. 9.1% with lixisenatide and 3.2% with placebo discontinued due to TEAES.

Allergic reactions: 7 patients experienced possible allergic reactions, 5 receiving lixisenatide and 2 receiving placebo. Two events, both with lixisenatide, were adjudicated as possible allergic events. One was urticaria which was assessed as possibly treatment related.

Cardiovascular events were reported for 4.5% receiving lixisenatide and 0.6% receiving placebo. A TEAE under the coronary artery disorders HLGT was reported for 1 patient receiving lixisenatide. This was not serious and did not lead to permanent discontinuation of treatment group. There were no coronary artery disorder events with placebo.

7.2.2.9. EFC6018: Monotherapy

Those analysed for safety: placebo (n=122) and lixisenatide (n=239). The percentage of subjects with TEAEs was: placebo 45.1% vs lixisenatide 53.6%. Permanent discontinuation was 0.8% (placebo) vs 3.3 % (lixisenatide).

Most frequent adverse events were vomiting 7.1% (lixisenatide) vs 0 (placebo); nausea 22.6% vs 4.6% (lixisenatide vs placebo); symptomatic hypoglycaemia 1.6% in each group none classified as severe); 4.6% had injection site reaction in the lixisenatide group; of these there were 2 subjects (0.8%) who were classified as having allergic reaction.

There were no differences in cardiac events. There were no reports of pancreatitis. There were no deaths.

7.2.2.10. LTS10888: Monotherapy

This is of limited relevance as it was open label and only undertaken in one country, Japan.

There were 69 subjects included. Mean exposure to lixisenatide was longer than in some previous studies, being 438 (160) days. 85.5% had TEAEs at 24 weeks; at 76 weeks it was 91.3%.

There were no deaths reported during the study.

74% had GIT events at 76 weeks; there were 14.5% withdrawals at 76 weeks. Of these 4.3 % withdrew because of nausea and the same percentage due to decreased neutrophils.

During the 76-week treatment period, 5 (7.2%) patients in the pooled titration group had 6 events of symptomatic hypoglycaemia none of which were severe or led to discontinuation. During the 76-week treatment period, 5 patients had a TEAE adjudicated as an allergic reaction; one event of urticaria was adjudicated as possibly related to study treatment and led to discontinuation. During the 76-week treatment period, no patients had events of changes in pancreatic enzymes, lipase, or amylase reported as suspected pancreatitis. CV events were reported in 2 patients (ventricular hypokinesia and silent myocardial infarction).

7.3. Patient exposure to lixisenatide

The total number of subjects exposed in the Phase 2 and 3 studies were: lixisenatide (n=3304) and placebo (n=1232); active comparator (n=548).

7.4. Overview of adverse events

An overview of TEAEs experienced by patients over the total treatment periods in the phase 3 placebo controlled studies (EFC6014, EFC10743, EFC6015, EFC6018, EFC6016 and EFC10887) is provided in the dossier.

In the placebo controlled studies, TEAEs were as follows in the lixisenatide n=2127 and placebo n= 1061groups respectively: GIT (48.3% vs 25.8%); nausea (28.5 vs 10%); hypoglycaemia was 19.7% vs 17%.

Deaths were 0.36% (lixisenatide) vs 0.47% (placebo). Discontinuations were 9.6% vs 5.18%. TEAEs leading to permanent discontinuations were 7.4% in the lixisenatide group and 3.2% in the placebo group. These imbalances were primarily due to TEAEs in the GIT disorders (4.6% in the lixisenatide group vs 0.7% in placebo; in the lixisenatide group nausea was 3.2%, vomiting 1.2%; this was 0% in placebo).

7.4.1. Active comparator studies:

Table 30: Overview of TEAEs in studies with lixisenatide and an active comparator

	EFC6019		PDY10931		EFC10780	
	Lixisenatide N=318	***Exenatide N=316***	***Lixisenatide N=77***	***Liraglutide N=71***	***Lixisenatide N=158***	***Sitagliptin N=161***
TEAEs total treatment period	257 (80.8%)	264 (83.5%)	45 (58.4%)	52 (73.2%)	101 (63.9%)	98 (60.9%)
SAEs	26 (8.2%)	22 (7.0%)	0	0	3 (1.9%)	3 (1.9%)
Deaths	3 (0.9%)	3 (0.9%)	0	0	0	0
Treatment discontinuations	45 (14.2%)	45 (14.2%)	2 (2.6%)	2 (2.8%)	4 (2.5%)	5 (3.1%)

PDY10931 was a phase 2 study over 4 weeks to compare the PD effects of lixisenatide and liraglutide. Hence safety data from this are limited. The phase 3 studies, EFC6019 and EFC10780, were undertaken over 24 weeks. There was an extension period for study EFC6019.

Overall, there were no clinically significant differences seen between groups.

In relation to the Phase 3 studies, the following are of note:

Deaths: In the Phase 2/3 studies, 16 deaths were reported in the lixisenatide group. (This analysis included placebo and active controlled studies; also one uncontrolled study). The patient's details are provided on these subjects. The details were as follows: Malignancy-4; completed suicide-1; stroke, CVA-2; haemothorax-1; multi-organ failure-1; cardiac death, myocardial infarction-5; sepsis-1 and TB-1.

Based on the numbers it was not possible to detect any causality to the study drug.

Cardiac events in the placebo controlled studies: It is stated that in order to respond to novel health authority requirements which became effective during the phase 3 studies, an adjudication process by an independent Cardiac Adjudication Committee was implemented. This Committee was an independent body.

In the pooled placebo studies cardiovascular events (SOC) were 6.3% in lixisenatide vs 4.3% in placebo. SVT (highest level term) was 0.7% vs 0.2%; palpitation (preferred term) 1.5% vs 0.8%> there were no significant trends with SBP or DBP. ECG did not reveal any significant trends.

A Serious TEAE for cardiac SOC is given below, in the placebo controlled studies:

Table 31: Serious TEAEs: Cardiac SOC

Term	Placebo	Lixisenatide
Cardiac disorders	21 (2.0%)	30 (1.4%)
Acute myocardial infarction	5 (0.5%)	7 (0.3%)
Coronary artery disease	5 (0.5%)	6 (0.3%)
Angina unstable	2 (0.2%)	5 (0.2%)
Atrial fibrillation	2 (0.2%)	3 (0.1%)
Myocardial infarction	3 (0.3%)	3 (0.1%)
Atrioventricular block complete	0	2 (<0.1%)
Cardiac failure congestive	1 (<0.1%)	2 (<0.1%)
Angina pectoris	4 (0.4%)	1 (<0.1%)

The numbers are too small to show clear trends. Any event related to lixisenatide therapy would only manifest in large post market studies.

There was a CV meta-analysis undertaken. All randomised patients were analysed. (There were 2127 subjects randomised to lixisenatide); mean duration of diabetes was 8 years. CV risk factors- obesity ≥ 30 kg/m^2 (52.6 vs 50.7), hypertension 67 vs 65%; dyslipidaemia 49.3% vs 53.2%; smokers 33% in each grup; history of major CV events was 10.8% vs 11.9%. The major CV events sent to CAC were adjudicated for the following categories: MI, stroke, CV death, hospitalisation for unstable angina, hospitalisation for heart failure and coronary revasularisation procedure. The results from the 6 Phase 3 placebo controlled studies are as follows:

There was a total of 172 potential CV events that occurred post randomisation from 107 patients (3.2) in the lixisenatide group and 3.7% in the placebo group.

The hazard ratio (95% CI vs placebo): 1.26 (0.65, 2.47).[23]

All major cardiovascular events reported by investigators did not show any difference between lixisenatide and placebo; HR was 0.87 (0.58, 1.31).

[23] Sponsor clarification, provided in the response to the CER: hazard ratio is for the primary composite endpoint (first occurrence of CV death or non fatal MI or non fatal stroke or hospitalization for unstable angina that was positively adjudicated by CAC).

Symptomatic hypoglycaemia: In the monotherapy studies (vs placebo), the incidence was 1.6% in the placebo and 1.7% in the lixisenatide group. There were no severe hypoglycaemic episodes reported in this group.

In the studies (EFC 6014 and 10743) where there was background metformin use the incidence of symptomatic hypoglycaemia was 0.6% in the placebo group and 3.1% in the lixisenatide group; here, those with blood glucose < 60mg/dL were 3.0% in the lixisenatide and 0.3% in the placebo group. In the exenatide controlled study (EFC 6019) with background metformin, the incidence was greater with exenatide: those with blood glucose < 60mg/dL were 2.2% in the lixisenatide group and 6.3% in the exenatide group. In the sitagliptin comparator study, these figures were similar between groups being 1.6%.

With sulfonylurea as background (subpopulation in EFC 6015) those having blood glucose < 60mg/dL were 4.3% in placebo and 12.5% in the lixisenatide group. In the metformin and sulfonylurea group (subpopulation EFC 6015) the rates in placebo and lixisenatide were 9.2% vs 12. 1%.

Basal insulin and metformin as background (EFC6016) those with blood glucose < 60mg/dL were: placebo 21.0% vs lixisenatide 26.5%. Basal insulin alone (EFC 10887 in a subgroup) the levels were 23.9% in placebo and 28.3% lixisenatide. Basal insulin and sulfonylurea (EFC 10887), the levels were 42.6% in the lixisenatide group and 18.9% in the placebo group.

Symptomatic hypoglycaemia increased when lixisenatide was added to sulfonylurea and also to basal insulin.

Injection site reaction: ARAC assessment (see next section) was conducted in all controlled studies where lixisenatide n= 2881 and all comparators n=1758: injection site reaction was higher (1%) in the lixisenatide group and 0.2% in the comparator groups.

Allergic or hypersensitivity reactions: These reactions were adjudicated by ARAC. This committee was independent of sponsor and investigator and blinded to the treatment. The prespecified diagnoses were hives, angioedema, anaphylactic shock and reaction and other; there also were objective definitions of severity.

In the main treatment period in the Phase 3 placebo controlled studies 25 patients (1.2%) in the lixisenatide group and 7 patients (0.7%) in the placebo group were adjudicated as having allergic reactions. The events that were possibly related to the IP, urticaria (0.2%, n=6) vs 0.1% in all comparator groups; angioedema (<0.1%, n=3) in lixisenatide group vs 0.1% in all comparator groups, anaphylactic reaction 7 (0.2%) vs none in the comparator groups. Similarly, there was one local reaction (Type IV hypersensitivity) in the lixisenatide group. It is stated that a small % were only severe; this proportion that was classified as 'severe' should be stated by the sponsor in response to this report.[24]

Pancreatitis: Pancreatitis was coded as Class 2- pancreatitis, acute and chronic pancreatitis; Class 1 was abdominal symptoms that could potentially be pancreatitis. Class 3-was abdominal symptoms with elevated lipase and amylase. The following were observed:

Table 32: Incidence of pancreatitis according to severity

	Lixisenatide n=2682	Placebo n=1232
Class 2	5 (0.18%)	1 (0.08%)
Class 1-3	38 (1.2%)	16 (0.9%)

[24] In the response to the CER, the sponsor clarified that most events were classified as severity grade 1 (14 events) or 2 (6 events) by ARAC. One event each were classified as severity grade 3 or 4, and none were classified as severity grade 5 or 6.

Adverse events relating to thyroid C cell proliferation: This was seen in 0.7% in the lixisenatide and in all comparator groups. Thyroid neoplasm was 0.3% (lixisenatide) and 0.2% (placebo) respectively. There were no cases of thyroid cancer reported in the lixisenatide groups.

Calcitonin level: This was not done in ACT6011, PDY 6797, DRI6012, PDY 10931 and EFC 6018. The measurement of serum calcitonin measurement was implemented as a protocol amendment in the Phase 3 studies when in progress (as such there are no baseline values in most patients). Values ≥50ng/L was as follows: 0.4% in the lixisenatide group vs 0.1% in placebo in pooled controlled studies. The individual patient details did not reveal any untoward event relating to thyroid neoplasia. When blood calcitonin ≥ 20 ng/L was examined it was 1.2% vs 0.9%.

There was one renal failure in the lixisenatide group.

Immunogenicity: Data on anti lixisenatide Ab status and safety was assessed where available in the efficacy and safety evaluation of individual CSRs. This comprises data from the following phase 3 placebo-controlled studies: EFC6015, EFC6016, EFC6018, EFC10743, and EFC10887.

Samples for assessment were collected at baseline, weeks 2 and 4, and the primary endpoint visit (week 24 or week 12 for EFC6018). Data at Week 76 were also available from EFC6015, EFC6016 and EFC10743, as well as data at Week 100 for some patients. A patient was defined as anti-lixisenatide Ab+ve during the entire study if they were +ve at any visit.

The antibody level increased with time. With lixisenatide, at baseline a low incidence (5.4%) of Ab+ve status was reported but concentration levels were < LLOQ in most of these patients in whom it was assessed. The proportion of patients with Ab+ve status increased over time up to week 24 (9.4% at week 2; 37.3% at week 4; 57.7% at week 12 and 70.7% at week 24) and then remained stable up to the end of treatment. 98% remained below the LLOQ.

The relationship of antibody status to adverse events was difficult to determine due to the numbers involved. However, there was a trend in relation to injection site reaction and allergic events:

Table 33: Antibody status and selected AEs

	Antibody +ve	Antibody -ve
Injection site reaction (%)	4.7	2.5
Allergic events (%)	2.1	1.6

7.5. Evaluator's overall conclusions on safety

The absolute adverse event incidence with lixisenatide can be ascertained from the monotherapy study EFC 6018 where lixisenatide (n=239) was compared to placebo (n=122), in treatment naive patients. The percentage of TEAEs was 53.6% (lixisenatide group) vs 45.1% in placebo. The most frequent event was vomiting (7.1%) vs 0 in placebo. In this study symptomatic hypoglycaemia was 1.6% in each group. Injection site reaction was 4.6% vs 0 in placebo, in this study.

The dose selection study DRI6012 suggests a dose response in relation to TEAEs. In relation to the adverse events reported, it appears that the 20 µg is the optimum dose of lixisenatide.

Add on to metformin (EFC 6014, EFC 10743 and EFC 6019): dual therapy:

In the two placebo controlled studies, 832 subjects were included in the lixisenatide group and 330 in the placebo group. The mean duration of treatment in these studies have been over 500

days. The studies have used the dose proposed in the draft PI and the population reflects the target population.

Nausea has been a common TEAE being 25-38% and vomiting 13-18%. The adjudicated allergic reactions were seen in 1.6% to 3.8% in the lixisenatide vs 1.6% in the placebo groups. There was also one report of anaphylactic reaction in the lixisenatide group. Symptomatic hypoglycaemia varied in these studies with lixisenatide always exceeding the placebo group.

The study vs exenatide (EFC 6019) where 319 were given lixisenatide and 316 given exenatide, provides valid comparison of drugs in the same class. The mean duration was over 410 days. Symptomatic hypoglycaemia was higher in the exenatide group (14.6% vs 5.0%) in the lixisenatide group. Adjudicated allergic events, however were higher in lixisenatide group being 1.9% vs 0.9%.

Data to support use with sulfonylurea (EFC 6015) as dual therapy is only on a subpopulation in this study that involves placebo (n=46) and lixisenatide (n=88). This, in the opinion of the evaluator, is inadequate for a new chemical entity.

Add on to metformin and sulfonylurea (EFC 6015) as triple therapy

Here the number involved were 285 in the placebo group and 574 in the lixisenatide group; the mean duration was 570 days. The events were broadly similar to the previous studies. The addition of sulfonylurea appeared to increase the hypoglycaemic events (24.6% in lixisenatide group compared to previous studies on metformin as dual therapy; see above for reported rates). This is an expected finding.

Add on to basal insulin ± metformin or sulfonylurea (EFC 6016 and 10887)

This study (EFC 6016) included 167 subjects in the placebo group and 328 in the lixisenatide group and the mean duration was 510 days. The adverse profile was similar to the previous studies. Study EFC 10887 was a study of similar design conducted in Asian subjects. This study included insulin and sulfonylurea in 70% of the subjects. Hypoglycaemia was higher in the lixisenatide group vs placebo (43.5% vs 23.6%).Cardiovascular events were also higher being 4.5% vs 0.65%. The data to support lixisenatide use with insulin alone is in 30% of EFC 6016 and EFC 10887. The issue with this small number is that it does not represent the target population in Australia adequately.

Adverse events of concern

In relation to adverse events of concern to drugs for diabetes mellitus and of this drug class cardiac events showed a marginal increase in the lixisenatide groups vs placebo (2.0% vs 1.4%). The individual events are too small in number; their significance can only be ascertained in large post-market studies.

There was also a higher incidence of symptomatic hypoglycaemia in lixisenatide in the placebo controlled studies. There was also an increase seen in add on SU study and basal insulin studies. This has been addressed in the PRECAUTIONs section of the PI.

There are also hypersensitivity reactions above placebo (1.2% vs 0.7%). Injection site reaction was higher with lixisenatide (1% vs 0.2%).It is not possible to state whether these are due to the occurrence of antibodies.

8. Clinical questions

8.1. Questions and evaluation of sponsor responses

The clinical questions asked by the TGA and the evaluation of the sponsor responses to these are provided below.

Absolute Bioavailability Study

Question: The justification for not conducting an absolute bioavailability study does not address the question of why intravenous administration was not undertaken. Please provide the reasons - but not new data for this - (e.g. pharmaceutical or safety reasons).

Response: This is essentially similar to the justification provided by the sponsor and discussed under *Bioavailability*, above, in this report. It also states that, "the only (intrinsic) factor that was identified as having a marked impact on the disposition of lixisenatide (but not on the efficacy) is the development of anti-lixisenatide antibodies. It is important to note that the development of anti-lixisenatide antibodies is believed to impact the distribution and clearance of lixisenatide, but not its absorption."

The sponsor concludes that taking into account the well established use of subcutaneous formulations for diabetes treatment and the scope and quantum of information provided in the clinical dossier is adequate for assessment of lixisenatide despite the absence of an absolute bioavailability study.

Evaluator's comment: As previously stated under *Bioavailability*, above, no valid reasons are put forward. The pharmacokinetics is not well defined and it is not known if this product is optimally formulated. It is not known if there is degradation at the site of injection; the lack of equivalence in relation to C_{max} observed in relation to thigh vs abdomen in study BDR 6864 is not satisfactorily explained. This is a significant deficiency as these sites are the proposed sites of injection.

Site of Administration/Absorption

Question: "Please consider providing additional information in the PI to indicate that absorption from the thigh is different to that in the abdomen and arm."

Response: The Absorption subsection in the Pharmacokinetics section of the draft PI has been updated to reflect the results of Study BDR 6864.

Evaluator's comment: The modification in the draft PI includes only the T_{max}. It is recommended that the C_{max} test/vs reference point estimate and the 95% CI be included from this study so that there is a factual presentation of the results. In addition, the CMI indicates that injections can be administered into the arm, thigh and abdomen. Modifications of this also are necessary.

Elderly Patients

Question: In the special populations section of the PI, for elderly patients it is stated that: "Age has no clinically relevant effect on the pharmacokinetics of lixisenatide based on a pharmacokinetic study conducted in elderly non diabetic subjects."

The sponsor was requested to justify this statement and consider inclusion of additional text to provide more information on data from use of lixisenatide in the elderly. The associated statement in the precautions section should be addressed concomitantly.

Response: The sponsor reiterates that the results of study POP11814 show a trend for an increase in the AUC and half life with increasing age. Results of a meta- analysis of data from the 5 placebo controlled studies on HbA_{1c} change by age categories (< 65, ≥ 65) and (<65, ≥ 65 to < 75, ≥ 75 to < 85 and ≥ 85 years [1 patient in placebo group]) are presented. With lixisenatide,

the LS mean change in HbA1c from baseline was -0.79% for adult patients < 65years, (n=1,660), and -0.95% in elderly patients aged ≥ 65 years (n=352). Compared with placebo, the LS mean change from baseline in HbA1c was -0.22% in patients < 65years (n=786) and -0.31% in patients aged ≥ 65 years (n=234).

Hence, the LS mean differences versus placebo were similar in adult and elderly patient groups: -0.56% in adult and -0.66% in elderly patients. Data for the other subgroups suggested similar changes though for patients > 75 years (43 patients who received lixisenatide and 31 who received placebo) the analysis is limited by the number of patients in the lixisenatide and placebo groups.

In relation to safety, all Serious TEAEs by age group (< 65 and ≥ 65 years) and all TEAEs leading to discontinuation by age group (< 65 and ≥ 65 years) were also discussed.

The following is noted for the main treatment period,

- In patients ≥ 65 years, 71.8% with lixisenatide reported TEAEs and 59.0% with placebo; in patients < 65 years, 68.8% in with lixisenatide and 63.2% with placebo reported TEAEs.
- In patients ≥ 65 years, TEAEs leading to discontinuation were reported in 12.7% with lixisenatide and 4.5% with placebo- this was due to a high incidence of nausea; in patients < 65 years there were 6.2% with lixisenatide and 2.8% with placebo with TEAEs leading to discontinuation.
- There were no imbalances by age between treatment groups for SAEs.

It is noted that the information for very elderly patients (≥ 75 years) is limited by the small number of patients in this age category.

The sponsor concludes that the pk analysis as well as efficacy and safety results of phase 3 studies support the statement that "age has no clinically relevant effect on the pharmacokinetics of lixisenatide". In response, the sponsor proposed an amended text in the draft PI under *Use in the elderly.* The results of the pk study **POP11814** are to be included in the final PI.

Evaluator's comment: This is accepted.

Renal Impairment

Question: In the special populations section of the PI, for renal impairment it is stated that, "*There were no relevant differences in mean clearance, C_{max} and AUC of lixisenatide between subjects with normal renal function and subjects with mild (creatinine clearance: 50-80 mL/min) or moderate (creatinine clearance: 30-50 mL/min) impaired renal function. Mean C_{max} and AUC increased with further increases in the degree of renal impairment.*"

As renal impairment is a known complication of diabetes and a low dose of lixisenatide was used in the study, the sponsor was requested to justify the proposed statement in the PI and consider inclusion of additional text to provide more information on data from use of lixisenatide in patients with mild, moderate and severe renal impairment. Also, it was indicated that the associated statement in the precautions section should be addressed concomitantly.

Response: A meta-analysis (based on the combined data from the 6 placebo-controlled studies) for change in HbA1c for patients with mild or moderate renal impairment (assessed by creatinine clearance of 50-80 ml/min for mild and ≥30-<50 ml/min for moderate renal impairment at baseline) is presented.

The LS mean difference versus placebo in HbA1c in patients with normal renal function, or mild or moderate renal impairment did not reveal a relevant difference in HbA1c change at Week 24: LS mean differences versus placebo were -0.56% (normal renal function), -0.63% (mild renal impairment) and -0.87% (moderate renal impairment). The higher LS mean difference for moderate renal impairment is attributed to an increase in HbA_{1c} (LS mean change=0.04%) in the associated placebo group whereas in the 2 other placebo groups decreases (LS mean -0.28%

for mild renal impairment and -0.22% for normal renal function) were seen. The absolute LS mean changes for HbA1c in lixisenatide groups were similar across all levels of renal function (normal renal function: -0.79%, mild renal impairment -0.91%, and moderate -0.95%). It is considered that these data support the findings in patients without T2DM.

Data on safety by baseline renal function showed the following:

- The phase 3 placebo-controlled studies included 565 patients with mild impairment (366 with lixisenatide and 199 with placebo), 48 with moderate impairment (28 with lixisenatide and 20 with placebo) and 3 patients with severe renal impairment all with placebo.
- Patients with mild or moderate impairment experienced slightly more TEAEs (mild renal impairment 84.7% and moderate 89.3% with lixisenatide compared to 73.4% (mild) and 75.0% (moderate) with placebo, respectively) than patients with normal renal function (80.4% with lixisenatide and 74.6% with placebo).
- With mild renal impairment the incidence of TEAEs were generally balanced between lixisenatide and placebo groups, except for nausea, vomiting, and hypoglycaemia; there were no imbalances in the incidence of SAEs; during the entire treatment period, more patients with lixisenatide 60 (16.4%) experienced TEAEs leading to treatment discontinuation than with placebo, 10 (5.0%).
- With moderate renal impairment, the incidence rates of TEAEs were generally balanced between lixisenatide and placebo groups, except for nausea, vomiting, headache, and hypoglycaemia; SAEs were reported by 4 patients, 2 receiving lixisenatide and 2 receiving placebo; TEAEs)leading to discontinuation were reported by 8 patients, 5 receiving lixisenatide, and 3 receiving placebo.

The sponsor concluded that based on these data, the administration of lixisenatide to patients with mild or moderate renal impairment does not lead to an increased risk of SAEs or hypoglycaemia. Notwithstanding this, it is noted that there were a limited number of patients with moderate renal impairment included in these placebo-controlled phase 3 studies, and this information will be reflected in the *Precautions* and *Dosage and Administration* sections of the updated PI. Also, results of the phase 1 study conducted in nondiabetic subjects with renal impairment (POP6053) will be provided in the *Special Populations* subsection of the *Pharmacokinetics* section in the PI.

Evaluator's comment: There are no subjects included in the studies with severe renal impairment: this should be a CONTRAINDICATION.(Currently, this is not the case).

Those with moderate renal impairment: There are only 23 subjects (1.08%) in a total of 2119 who had lixisenatide in the placebo controlled studies who are included in the efficacy analysis; 28 (1.3%) in the safety analysis. This number is inadequate to support safety or efficacy in subjects with moderate renal impairment; thus, safety is not established in this subgroup and it should also be CONTRAINDICATED. (At present, there is a statement under Dosage and Administration that states Lyxumia should be used with caution in this population).

GIT effects were the commonly reported TEAEs SOC (53.6% vs 22.6% in placebo) in those with mild renal impairment. In the phase 3 studies, the incidence in the total population given lixisenatide was 41.3% , suggesting an increase in TEAEs in those with mild impairment. It is recommended that there should be a precautionary statement in the PI that these patients be followed up regularly for potential safety concerns.

The sponsor has agreed to include the findings of the pk study (POP6053). All pk results (C_{max}, AUC, t_{max} and $T_{½}$) in the subgroups should be provided. This should include some indication of scatter for the pk variables.

Clinical Trials

Question: In the subsection titled Body Weight in the clinical trials section of the PI, the following is stated:

"*Treatment of lixisenatide in combination with metformin, basal insulin and /or a sulphonylurea resulted in a body weight mean reduction up to 2.96 kg at the end of the main 24- week treatment period which was sustained in long term studies up to 2 years. The body weight reduction is independent from the occurrence of nausea and vomiting*."

Studies EFC6014, EFC6015, EFC6016, EFC10743 and EFC6019 are referenced as the data sources to support this statement. Results from these did not include a mean reduction up to 2.96 Kg. Also it was noted that, in the placebo controlled studies, there was a decrease with placebo with the difference in weight loss between placebo and lixisenatide about 1Kg. As this was a small loss and there was also a loss with placebo, the validity of claiming a clinically relevant weight effect and hence inclusion of the proposed statement were queried. It was considered that the sponsor should reconsider inclusion of this statement in the proposed PI.

Response: The sponsor notes that in the active-controlled study versus exenatide (**Study EFC6019**), the LS mean change (SE) in body weight from baseline to Week 24 was -2.96 kg (0.231) with lixisenatide and -3.98 kg (0.232) with exenatide. The mean (sd) body weight reduction was -2.83kg (2.98) with lixisenatide and -3.76 kg (4.08) with exenatide.

There is reference to the EMA guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus noting that this recommends that a new glucose-lowering agent should preferably show a neutral or beneficial effect on body weight.

It is indicated that the LS mean decrease in body weight from baseline ranged from 1.76 kg to -2.96 kg with lixisenatide in all phase 3 controlled studies (excluding study EFC10887 in (only) Asian patients who had a mean baseline BMI of 25.3 kg/m^2), and was generally significantly greater than in the placebo groups. The effects on body weight were observed in all therapeutic settings (add-on to metformin, SU with or without metformin and basal insulin with or without metformin). This body weight reduction can be considered as clinically relevant and beneficial for patients, and it is in the same range as what is usually observed with other GLP-1 receptor agonists. A reference is provided to support this statement and data from it are included in the response. Results of a meta-analysis of data from the 6 placebo-controlled studies are presented and are consistent with the range of results from individual trials. Based on these results and in order to clarify the initial text in the PI, the Sponsor proposes to give the body weight reduction according to treatment settings (i.e. either when lixisenatide is used in add-on to oral anti diabetics or in add-on to basal insulin) in the revised Clinical Trials section of the PI.

Evaluator comments: The sponsor's response is noted. However, the following statements are necessary in the draft PI.

No studies on appetite or weight loss have been conducted; this should be clearly stated in the PI.

There is a statement proposed that "*body weight is independent from the occurrence of nausea and vomiting*"; however, this has not been established in any studies and should be removed.

There are references to bodyweight reduction in individual study presentations in the draft PI. This should be removed as body weight is a secondary efficacy endpoint; if the sponsor wishes to include this, all secondary efficacy endpoint results should also be presented to factually represent the study findings. The statistical significance of these findings should also be included.

There should be a statement that, any claimed benefit is not validated with long term morbidity or mortality data.

Immunogenicity

This **Question** notes the proposed text in the PI on immunogenicity and, in particular, that this states that some Ab+ve patients had diminished efficacy. It was requested that the sponsor should indicate how this will be assessed if the product is approved for marketing and provide information on whether the Ab assay will be commercially available to assess efficacy failure.

Response: The following is noted.

Based on the meta-analysis performed on studies EFC6015, EFC6016, EFC10743, and EFC10887 submitted within the original dossier, there is no signal for a progressive decline in efficacy at Week 24 triggered by Ab status; the LS mean change in HbA1c was similar regardless of the patients' Ab status: LS mean (SE) of -0.81 (0.051) in Ab+ve patients and -0.83 (0.065) in Ab-ve patients. (In this data set 693/998 (69.4% were Ab+ve; 305/998 (30.6%) were Ab negative).

Those with antibodies were categorised into 4 quartiles based on the antibody concentration. The LS mean change in HbA_{1c} from baseline to week 24 was -0.18% (95% CI: -0.428 to 0.075) for the group of patients with the highest Ab concentration, which may indicate a trend for diminished efficacy in the limited number of patients (51/998) with the highest Ab concentration.

In the same meta analysis for results at week 76, the trend for diminished efficacy in patients with the highest Ab concentration is no longer observed; however, the change in HbA1c was somewhat less in Ab+ve than Ab-ve patients (LS mean change: -0.75 [SE 0.066] and -1.05 [SD 0.086], respectively). The reduction in HbA_{1c} by antibody concentration group was comparable among group 1 (LS mean change -0.68% [95% CI: -0.999 to -0.363%]) and group 4 (LS mean change -0.45% [95% CI: -0.783 to -0.124%]).

It is indicated that since submission of the original dossier, the Ab analysis for study EFC6014 has been completed; results of the 2 meta-analyses at weeks 24 and 76 including these data are similar to those in the previous pool of studies.

Also, an additional analysis based on the phase 3 placebo-controlled studies submitted in the original dossier (EFC6015, EFC6016, EFC10743, and EFC10887) was provided in the response using a converse approach to present the Ab concentration data by category of HbA1c change (change in HbA_{1c} < -1.2%, ≥-1.2 to < -0.4%, ≥-0.4% to < 0%, ≥ 0 to < 0.4%, ≥0.4%) in patients with quantifiable antibody concentration at weeks 24 and 76.

It was considered that these results show that the range of Ab concentrations is similar by category of HbA_{1c} change and noted that patients with relatively high Ab concentrations have a clinically relevant reduction in HbA_{1c}. Based on these data the sponsor considers that Ab concentration cannot predict HbA_{1c} change in an individual patient.

The sponsor concludes that based on the efficacy results for decrease in HbA_{1c} by Ab status and the analysis to assess whether Ab status and/or concentration is predictive for clinical efficacy, use of Ab measurement in clinical practice it is not recommended.

Therefore no commercial antibody assay is considered necessary since the main indicator of efficacy will remain the measurement of HbA_{1c}.

Evaluator comment: The following issues are of concern:

The sponsor has categorised into 4 quartiles, the number with varying concentrations of antibodies. They are referred to as groups, with group 4 having the highest concentration.

It is observed from the data, that the group with the largest concentration of antibodies showed the least magnitude of effect in terms of HbA_{1c} at 24 weeks. This was in the mITT group. This appeared to be maintained at 76 weeks. If data from study EFC 6014 (with recently completed findings on antibodies) is included, similar observations at 24 and 76 weeks are noted.

Hence, the sponsor has not addressed how it proposes to monitor for the potential lack of efficacy.[25]

Clinical Trials [PI text]

The question notes that in the subsection titled Glycaemic Control in the clinical trials section of the PI, it is stated that lixisenatide "demonstrated superior effect compared to placebo in reducing glycosylated haemoglobin (HbA1c) regardless of the background treatment and Lyxumia once daily showed a non inferior HbA1c reduction compared to exenatide twice daily. This effect on HbA1c was sustained in long term studies for up to 2 years."

It was noted that only a small proportion of patients were treated for 2 years. The sponsor was requested to modify the wording about the duration of effect to reflect the numbers treated for the various time frames.

The sponsor agreed with this and the PI has been updated accordingly.

Evaluator comment: This is accepted.

PK data in the Ab+ve subjects and the implications of these for PD and safety:

The **question** notes that for study ACT6011, the CSR presents pk data from the day 29 Ab-ve group with data from the day 29 Ab+ve group provided in an addendum. There was no discussion of the pk data for the day 29 Ab+ve group. A comparison of the mean values of selected AUC, Cmax, Tmax and half life data in the AB-ve and Ab+ve groups suggest a higher exposure to lixisenatide in the Ab+ve group irrespective of the dosing regimen. Results of the PD and safety analyses included all subjects with no separate data by Ab status. The higher lixisenatide exposure in Ab+ve subjects could have implications for the PD effect and safety. The sponsor is requested to consider the pk data in the Ab+ve subjects and the implications of these for PD and safety.

The **response** indicates that in Appendix C of the CSR, descriptive statistics is presented for the main PD parameter, the postprandial blood-glucose AUC[0:14h-4:55h] by Ab status for breakfast/lunch/dinner. An extract of these data showing the median AUC[0:14h-4:55h] at the 20µg dose (QD and BID) for breakfast/lunch/dinner by Ab status is provided and presented below.

Table 34: Median postprandial blood-glucose AUC[0:14h-4:55h] by antibody status for breakfast / lunch / dinner at dose level 20µg (QD and BID) in ACT6011.

AUC[0:14h-4:55h] [mg*h/dL]		Breakfast		Lunch		Dinner	
		ADA negative	ADA positive	ADA negative	ADA positive	ADA negative	ADA positive
Median	Placebo	883	-	870	-	553	-
	Lixisenatide 20µg QD	540	397	757	644	497	701
	Lixisenatide 20µg BID	535	395	705	706	379	506
Change from Baseline (Median)	Placebo	-113	-	23	-	1	-
	Lixisenatide 20µg QD	-519	-284	-276	-171	-181	-142
	Lixisenatide 20µg BID	-313	-311	-135	-226	-295	-239

This shows there are no major differences in the PPG between the Ab-ve and +ve patients in study ACT6011.

The data on TEAEs by Ab status is also presented. These show a higher frequency of TEAEs in Ab+ve patients however the numbers are small.

[25] In the response to the CER, the sponsor stated: Usual standard of care recommends the assessment of HbA1c every 3 months in patients with type 2 diabetes (Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes, Diabetes Care, Vol 35, June 2012). This would detect potential lack of efficacy in patients administered over a prolonged period.

Evaluator comment: It is agreed that there are no major differences in the PPG data for Ab-ve and +ve subjects and the sponsor response is accepted. Of note however, these are small patient numbers and nearly 50% in the QD and BID groups were Ab+ve.

Data Query: EFC6014

The question notes that in the CSR for study EFC6016, it is indicated there were no protocol deviations resulting in a patient being excluded from the mITT population. However, the patient numbers in the results of the analysis for the primary efficacy variable are < those in the mITT. Please explain this apparent discrepancy.

Sponsor response: This indicates that 327 of 329 randomized patients in the lixisenatide and 166 of 167 placebo patients were included in the mITT population (5.3.5.1 EFC6016 CSR page 61 and page 72).

Evaluator comment: Results of the analysis for the primary efficacy variable in CSR table 12 on page 72 indicates there were 158 patients who received placebo and 304 who received lixisenatide. The discrepancy has not been explained.

Data Query: EFC10887

The question notes that in the CSR for study EFC10887, data provided for the changes in the daily basal and total insulin doses from baseline to week 24 are the same. Please explain why the data provided for the daily basal and total insulin doses are the same.

Sponsor response: As in this study only basal insulin was allowed as background therapy the 2 analyses provided the same information. The results from the analysis of the change in daily total insulin dose are identical to those from the analysis of the change in daily basal insulin dose due to the fact that the rescue insulin usage was excluded from the analysis.

Evaluator comment: This is accepted.

Data Query: TES6865

The question notes that in the CSR for study TES6865, it is stated that 3 of the 4 subjects who discontinued the study were replaced. However, the analysis populations and subject numbers in the results are consistent with the numbers after taking into account those who discontinued. They do not appear to include the replacement subjects, x 2 with lixisenatide 20µgQD and x 1 with lixisenatide 30µgBID. These numbers are potentially material given the small numbers of subjects in each group. Please clarify this discrepancy.

Sponsor response: The sponsor response provides a detailed answer to this question explaining why discontinued patients were included in the analysis populations.

Evaluator comment: This is accepted.

9. Benefit-risk assessment

9.1. Assessment of benefit

To support add on to metformin there are two placebo controlled studies with an initial 6 months double blind period which shows lixisenatide is efficacious (compared with placebo). This was conducted on T2DM on maximum dose of metformin. The statistically significant superiority over placebo was maintained over 24 weeks. One study which had an extension phase up to 76 weeks also showed that the efficacy was maintained over the entire period. The secondary efficacy endpoints relating to glucose endpoints showed similar trends. The reduction in body weight over 6 months ranged from -2.0 to -2.6 kg. The placebo effect was -1.6 kg. The change in HbA1c at 6 months was approximately 0.8% in the lixisenatide group.

The active controlled study (vs exenatide) was also of similar design. This was designed as a non-inferiority study. Whilst this study showed non-inferiority in relation to HbA_{1c}, the effect was greater with exenatide. The non-inferiority margin was also wider than that stipulated in the EU Guideline. Superior trends were also seen with the secondary efficacy endpoints.

To support add on to metformin and sulfonylurea (triple therapy) there was one pivotal study (**EFC 6015**) which recruited the target population and showed statistical superiority over placebo over 6 months. There was a subpopulation in this study that included sulfonylurea + lixisenatide only (dual therapy). The numbers were small and inadequate to support this indication in relation to efficacy and safety; (45 in the placebo group and 91 in the lixisenatide group which was approximately 16% of the entire population).

There were two placebo controlled studies that supported the use of lixisenatide as add on to basal insulin. Stable dose of insulin (>30 U) and metformin (≥1.5 g) reflected the target population that would require further add on therapy. The second study was conducted in Asia and included Asian patients and thus, did not reflect the target group in Australia; this combination is not generally a recommended combination used in Australia. At 6 months, there was statistically significant difference over placebo in relation to HbA_{1c}. Maximum effect was seen at 12 weeks, then a waning of effect over 24 weeks was seen. Secondary efficacy endpoints showed similar changes; there was a reduction in the insulin dose seen. There was a tendency to decreased HbA_{1c} in those with the presence of antibodies. There is a request for the use of lixisenatide as add on to insulin monotherapy. The number of those given lixisenatide together with insulin is insufficient (20% in the first study and 30% in the second study) to support the efficacy and safety for this indication. Insulin is not generally used to treat T2DM; if there is contraindications to oral diabetic agents that would warrant such use, this population has not be tested in this study.

9.2. Assessment of risk

In relation to risks, the common effects were nausea and vomiting. There were adjudicated hypersensitive reactions which were higher than placebo (1.2% vs 0.7%). A higher increase of symptomatic hypoglycaemia was observed in the sulfonylurea study and also basal insulin studies. There was an increase in the hypersensitivity reactions and injection site reactions in those with antibodies. The relationship cannot be ascertained on the numbers involved; larger post-market studies are required to assess this. Cardiovascular effects were also higher (4.5% vs 0.65%). These risks are addressed in the PI and it is the evaluator's opinion that these are adequate provided the recommendations regarding the PI[26] are adopted by the sponsor.

9.3. Assessment of benefit-risk balance

As discussed under *Impaired renal function* in section 3.2.2.2, there need to be statements included regarding renal impairment in the PI.

Overall, there is a favourable risk benefit profile for the following indications; in combination with:

- metformin, or
- a combination of metformin and a sulphonylurea,

In combination with a basal insulin:

- in combination with metformin, or
- in combination with a sulphonylurea.

[26] The sections on PI and CMI are not included in this extract from the CER.

There is inadequate evidence for combination therapy with sulfonylurea; or in combination therapy with insulin alone.

10. Recommendation regarding authorisation

The following indications are recommended to be approved.

(Lyxumia) is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in patients not adequately controlled ~~on oral antidiabetics and/or basal insulin:~~ with diet and exercise, in combination with the following oral antidiabetics:

- metformin,
- ~~a sulphonylurea, or~~
- a combination of metformin and a sulphonylurea,

In combination with a basal insulin:

- ~~alone,~~
- in combination with metformin, or
- in combination with a sulphonylurea

The data to support the use with sulfonylurea is inadequate to support efficacy and safety of the proposed dual therapy.

The data to support the use with insulin (alone) is inadequate to support efficacy and safety of the proposed dual therapy.

11. References

1. Nauck MA. Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. *Am J Med*. 2011; 124(1 Suppl):S3-18.
2. Salehi M *et al*. Effect of endogenous GLP-1 on insulin secretion in type 2 diabetes. *Diabetes* 2010; 59:1330-7.
3. Vella A *et al*. Lack of effect of exendin-4 and glucagon-like peptide-1-(7,36)-amide on insulin action in non-diabetic humans. *Diabetologia*. 2002; 45:1410-15.

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