28 November 2012
EMA/CHMP/703852/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lyxumia

International non-proprietary name: lixisenatide

Procedure No. EMEA/H/C/002445/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ANCOVA	analysis of covariance
ARAC	allergic reaction assessment committee
AUC	area under the concentration curve
BID	twice daily
bpm	beats per minute
CAC	Cardiovascular Events Adjudication Committee
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CLCR	creatinine clearance
CLR	renal clearance
Cmax	maximum concentration
CSR	clinical study report
CV	cardiovascular
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
EMA	European Medicines Agency
FPG	fasting plasma glucose
GBEF	gall bladder ejection fraction
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide 1
HbA1c	glycosylated hemoglobin
HLGT	high level group term
HLT	high level term
ICH	International Conference on Harmonisation
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LS mean	least squares mean
MAA	marketing authorization application
MACE	major adverse cardiac events
MAT	mean absorption time
MI	myocardial infarction
mITT	modified intent-to-treat
OC	oral contraceptive
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNWT	predicted normal weight
PPG	postprandial plasma glucose
PT	preferred term
QD	once daily
SAE	serious adverse event
SU	sulfonylurea
TEAE	treatment emergent adverse event
T2DM	type 2 diabetes mellitus

TZD	thiazolidinedione

1. Background information on the procedure

1.1. Submission of the dossier

The applicant sanofi-aventis groupe submitted on 27 October 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lyxumia, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 November 2010.

The applicant applied for the following indication:

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:

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 legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/225/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/225/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance lixisenatide contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 15 November 2007 (including clarifications on 18 January 2008) and on 24 June 2010. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Sanofi-Aventis Deutschland GmbH
Brüningstrasse 50, Industriepark Höchst
65926 Frankfurt am Main
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Kristina Dunder** Co-Rapporteur: **Walter Janssens**

CHMP Peer reviewers: Pieter de Graeff and Agnes Gyurasics

- The application was received by the EMA on 27 October 2011.
- The procedure started on 16 November 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 03 February 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 03 February 2012.
- During the meeting on 15 March 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 March 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 May 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 June 2012.
- During the CHMP meeting on 19 July 2012, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 September 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 1 October 2012.
- During the CHMP meeting on 18 October 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 24 October 2012.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 31 October 2012.
- The Rapporteurs circulated an updated Assessment Report on 9 November 2012.
- During the meeting on 15 November 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Lyxumia.
- The CHMP adopted via written procedure on 28 November 2012 the revised CHMP Opinion and Assessment Report to include further details in the assessment report.

2. Scientific discussion

2.1. Introduction

Problem statement

Type 2 diabetes has a complex pathophysiology characterised by deficient insulin activity arising from decreased insulin secretion secondary to beta cell failure, compromised insulin action in peripheral target tissues (insulin resistance), or a combination of these abnormalities.

The condition is a chronic widespread disease in the western world with an expected increased incidence worldwide. Type 2 diabetes accounts for approximately 90% of individuals with diabetes, has its onset usually in adulthood but is seen in growing numbers of children, and is typically associated with excess body weight and physical inactivity. It is well known that patients with type 2 diabetes are at increased risk of macro- and microvascular complications including cardiovascular morbidity and mortality. A major purpose of using antidiabetic agents is to reduce these risks.

According to current guidelines for the treatment of type 2 diabetes, the treatment target should be HbA1c ≤7 %. Diet modification and exercise typically form the first line of treatment, but eventually most patients need at least two different antidiabetic compounds during the course of pharmacological intervention to reach treatment goals. The treatment algorithm published by the European Association for the Study of Diabetes and the American Diabetes Association from 2012 recommends metformin and life style changes as first line treatment. In the case of therapy failure (HbA1c above target after 3 months), several treatment options are considered. Since all treatment alternatives are associated with different adverse event profiles and may not be tolerated by certain patients, it is of importance that clinicians have access to different options when treating patients with type 2 diabetes.

About the product

Lixisenatide is an activator of the receptor for Glucagon-like peptide 1 (GLP-1). GLP-1 is an endogenous peptide of the incretin peptide family, with multifaceted effects on glycaemic control. As a class, GLP-1 and its analogs are known to stimulate insulin release from the pancreatic islets (insulinotropic release), suppress glucagon secretion, delay gastric emptying, and reduce body weight. The 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 common dipeptidyl peptidase-4 (DPP-4) enzyme. To take advantage of the effects of GLP-1, two different approaches have been used to develop longer-acting therapies in humans: inhibition of the DPP-4 enzyme (DPP-4 inhibitors) and the development of human GLP-1 analogues resistant to the action of DPP-4 enzyme (GLP-1 receptor agonists).

Lixisenatide is a GLP-1 receptor agonist resistant to enzymatic cleavage by DPP-4. This results in a longer duration of action making it possible to use lixisenatide for therapeutic purposes. Lixisenatide is intended for use in the treatment of adults with T2DM in combination with oral antidiabetics and/or

basal insulin, ie. as an add-on to monotherapy (metformin, a sulfonylurea, or a basal insulin) or dual therapy (metformin and a basal insulin; metformin and a sulfonylurea; or a sulfonylurea and a basal insulin). Other GLP-1 receptor agonists in use in the treatment of adults with T2DM are exenatide and liraglutide.

Lixisenatide is administered once daily subcutaneously. The recommended maintenance dose is 20 micrograms once daily; this is achieved after a 2-week starting regimen of lixisenatide 10 micrograms once daily.

2.2. Quality aspects

2.2.1. Introduction

The medicinal product is available as a sterile solution for injection with dosage strengths of 10 µg and 20 µg to be administered subcutaneously. The active substance lixisenatide is a synthetic peptide.

The full composition for excipients is detailed in section 6.1 of the SmPC. The solution for injection is filled into a 3 mL cartridge which is integrated in a pen-injector. The two strengths 10 µg and 20 µg are differentiated by the colour of the pen (green and purple), features and label design.

2.2.2. Active Substance

Lixisenatide (INN) is a synthetic peptide containing 44 amino acids, which is amidated at the C-terminal amino acid. The sequence of the amino acids has been provided.

General properties such as physical characteristics (amorphous, hygroscopic, white to off-white powder), melting point, pH, IR, and UV analysis of the peptide (in accordance with the structure), solubility, stereochemistry (pure L-form) were presented. Polymorphism has not been observed.

The information on the active substance has been provided according to the Active Substance Master File (ASMF) procedure. An authorisation letter and a complete ASMF were provided for this marketing authorisation application. In addition, a Qualified person declaration is also submitted confirming that Lixisenatide is manufactured in accordance with the European Guidelines ICH Q7.

Manufacture

The manufacturing process of lixisenatide drug substance is a standard solid phase peptide synthesis and consists of multiple synthetic steps, followed by purification and lyophilisation. A flow diagram and a comprehensive narrative description of the process have been presented.

Further information on the manufacturing process and process controls is provided in the restricted part of the Active Substance Master File.

Adequate in-process controls are applied during the synthesis. Satisfactory specifications and control methods for starting materials, reagents and intermediates were presented.

Details regarding specifications, analytical procedures, validation and batch results applied to intermediates and starting materials are found in the restricted part of the Active Substance Master File.

The structure of lixisenatide was elucidated using the following methods: Mass spectrometry (MS), Peptide mapping, Amino acid analysis, Amino acid sequencing (Edman sequencing technique). In addition, lixisenatide was investigated by: Infra-red (FT-IR) absorption spectrophotometry, Ultraviolet-

visible absorption (UV) spectrophotometry, X-ray powder diffraction (XRPD), Circular dichroism (CD) spectroscopy and Nuclear magnetic resonance (NMR)-spectroscopy.

Furthermore, the functionality of lixisenatide, a GLP-1 receptor agonist, was determined using a cell-based potency bioassay. The suitability of the bioassay method was investigated extensively and found suitable. The bioassay shows an adequate correlation with the HPLC results of the assay determination however the HPLC method is considered superior for routine testing.

A comprehensive discussion is presented on impurities (including isomers, degradation products, genotoxic impurities, leachables and extractables, residual solvents) of lixisenatide determined by HPLC. The impurities were found below the qualification levels in line with ICH guidance and did not raise any toxicological concern.

Specification

The specification for lixisenatide included the following parameters: appearance of the active substance (visual), Identification (Amino acid sequencing by Edman method), mass identification (Ph.Eur.), Assay lixisenatide (HPLC), related substances (HPLC and HPLC-MS), High molecular weight proteins (HPSEC = high pressure size exclusion chromatography), Chiral purity (AAA = amino-acid analysis- GC), residual trifluoroacetic acid TFA (HPLC), acetate content (HPLC), residual solvents (GC), water content (Karl-Fisher), microbial examination (Ph.Eur.), bacterial endotoxins (Ph.Eur.). The specification was adequately justified including the absence of certain tests such as the cell-based bioassay in the routine controls.

Analytical methods were well detailed and non-compendial analytical procedures as well as the procedures for Water and Bacterial endotoxins were validated to demonstrate their suitability for their intended purpose.

Three production batches of lixisenatide drug as well as 19 development batches have been tested. The batch results are within the proposed specifications and show consistent quality attributes.

Lixisenatide is packed into amber glass bottles with airtight closing screw caps. Due to its sensitivity to light, lixisenatide has to be protected from light. The materials comply with the Ph. Eur. monograph on glass containers for pharmaceutical use (Ph. Eur. 3.2.1), and Commission Directive 2002/72/EC, relating to plastic materials and articles intended to come into contact with foodstuffs. The packaging is suitable for its intended use.

Stability

Stability studies were conducted on three pilot-scale batches of lixisenatide packed in the commercial container closure system under ICH long term (18 months at -20°C±5°C), accelerated conditions (6 months at +5°C±3°C) and stress conditions (1 month at +25°C±2°C/60%±5% RH) according to ICH *Q1A(R2).*

The analytical procedures are the same as those used for the control of the drug substance.

Photostability studies were performed in line with ICH *Q1B (*Sun-Test-ICH option 1*).*

Bottles were stored inverted, in order to enable product interaction with the liner during storage.

The stability batches of lixisenatide were tested on appearance (visual), assay lixisenatide (HPLC), related impurities 1 (HPLC), high molecular weight proteins (HPSEC), and water content (Karl Fischer). The HPLC method was a stability-indicating method for the related impurities.

Under long-term and accelerated conditions,no significant change could be observed in the tested parameters and Only a slight increase of impurities was noticed under accelerated conditions. During the stress studies, an increase of impurities was observed but the other parameters did not show any relevant changes.

The photostability studies showed that lixisenatide is photosensitive when exposed to intense light.

Long term data and accelerated data for all attributes show little or no change over 18 months. The stability results indicate that lixisenatide manufactured by the proposed supplier is stable and justify the proposed re-test period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim was to obtain a medicinal product containing lixisenatide taking into account the physico-chemical properties of the active substance and its compatibility with the excipients.

The pharmaceutical development of the finished product contains Quality by Design (QbD) element. During development it was decided to commercialize a 10 µg and 20 µg solution for injection taking the desired quality target product profile (QTPP) into account. This QTPP considers the required dosage form (ready to use solution for injection), dosage strength (10 µg and 20 µg), administration (subcutaneous, multiple), biocompatibility (acceptable local tolerability), efficacy and safety (throughout shelf life) and pharmacopoeial conformance. The critical quality attributes (CQA) were determined to be identity, assay, appearance, impurities, osmolarity, pH and microbial integrity. The potential impact of formulation components on the CQA has been evaluated throughout development and is depicted in a risk matrix presented in the dossier. The choice of the excipients for the final formulation followed a risk assessment approach in order to achieve the best formulation (i.e optimal stability, local tolerability, antimicrobial preservative effectiveness, viscosity to allow good syringeability). The suitability of all the parameters was demonstrated in the pre-formulation and stability studies.

The excipients were selected based on their compatibility with the active substance, their technical performance in the manufacturing process, the local tolerance of the drug product, their availability in pharmacopoeial grade and their suitability for parenteral use.

Glycerol is used as a tonicity agent. Methionine is used as a stabilizing agent for chemical stability of the drug product. Sodium acetate trihydrate is used as a buffer agent to ensure a pH of 4.5 together with hydrochloric acid as acidifying and sodium hydroxide as alkalizing agents. Metacresol is added as preservative to prevent growth of microorganisms as required by pharmacopoeias for multidose containers. Water for injections is used as a solvent and nitrogen as a process aid for filtration.

Pre-formulation investigations and drug product stability studies show that the chosen excipients are compatible with the active substance.

Since lixisenatide is a peptide, the molecule is rapidly degraded after oral administration by the digestive system and, therefore, has to be administered parenterally.

The composition of the drug product formulation was based on the possibility of having multiple doses, physical, chemical and microbiological stability of the drug product, and physiological compatibility upon administration.

For early clinical studies a lyophilizate (powder for solution for injection) had been developed. Advancing in development, a solution for injection has been developed. For phase 3 clinical

development, the formulation containing 20 µg solution for injection was used. The different doses were provided by varying the administered volume. To simplify the handling by patients, a fixed dose pen-injector was developed for the commercial drug product

The detailed compositions of the batches used in toxicological and clinical studies are provided in the dossier. The proposed formulations for commercialisation have been used in clinical studies and these clinical batches were manufactured according to the proposed manufacturing process.

No assay overages are applied but overfilling is applied so that each cartridge is completely filled (no headspace). The correct administration of the labelled volume (3.0 mL) by multiple doses is ensured with the disposable pen-injector.

Since the active substance is heat sensitive the manufacturing process is based on aseptic technique.

Extensive and sufficient information on the manufacturing process development has been provided in particular regarding the standard aseptic processing techniques, the excipients, the container and the sterilizing filtration.

No major changes of the manufacturing process occurred during scale-up and transfer of the process to the manufacturing plant.

The theoretical impact of process steps on critical quality attributes (CQA) was assessed based on prior scientific experience. It was demonstrated that pH adjustment, aseptic processing and sterile filtration were critical aspects of the manufacturing process.

Lixisenatide solution for injection is supplied in multidose containers. A disposable pen-injector was chosen to enable repeated dispensing of fixed doses according to the therapeutic requirements of the patient. The 3 ml cartridges are made of colourless type I glass (Ph. Eur.) to allow visual inspection of the content. The closures of the multidose containers are commonly used and provide good physical integrity and re-sealability properties. The packaging materials selected meet the requirements of the Ph. Eur. The suitability of the packaging was substantiated by the results of the stability studies. The pen-injector performance was demonstrated and complied with the corresponding ISO standards on pen-injectors. To confirm the suitability of the pen-injector, in-use stability studies as well as an extractable/leachable study were conducted. Results showed that the pen-injector should be kept at room temperature and that the impurities level exposure to impurities did not reach any toxicological concern at the administered dose in accordance with the ICH guideline to ICH Q3C EMEA/CHMP/QWP/251344/2006.

Testing for efficacy of antimicrobial preservation is performed in accordance with the Ph. Eur. monograph 5.1.3. All results met the A criteria for parenteral preparations. The preservative efficacy at the lower shelf life limit is guaranteed.

Compatibility testing with other products has not been performed, since mixing with other products is not allowed and there is no direct contact between lixisenatide solution for injection and the pen-injector.

Adventitious agents

No excipients of human or animal origin are used for the manufacture of the drug product.

Manufacture of the product

The manufacturing process comprises compounding, pH adjustment, pre-filtration, sterile filtration, aseptic filling and packaging.

The manufacturing process has been validated as follow: a bracketing design was chosen for the validation. This approach is based on the original plan to submit three dosage strengths (5 µg, 7.5 µg and 10 µg). It also covers the batch size range and the two manufacturing process variants. It includes 5 batches (pilot and commercial scale). The bracketing validation approach was accepted previously through EU scientific advice procedure. The present submission includes sufficient validation batches demonstrating that a robust process is in place. All the batches tested for the process validation were found compliant with drug product release specifications, demonstrating the physical, chemical and microbial integrity of the product during manufacture. Thus, the consistency of the filling procedure into cartridges was demonstrated.

All the excipients used in the formulation and preparation of lixisenatide solution for injection are described in the Ph. Eur. and tested according to their respective monograph. The excipients glycerol 85%, sodium acetate trihydrate, methionine, metacresol are additionally tested for bacterial endotoxins and microbiological quality. Container closure integrity has been demonstrated.

No novel excipients are used to manufacture the drug product

Product specification

Release and shelf-life specifications for Lixisenatide 10 µg and 20 µg solution for injection include the following tests: appearance (visual), appearance clarity and colour (Ph.Eur.), identification (HPLC), identification (HPSEC), identification of metacresol (HPLC), assay of lixisenatide (HPLC), related substances (HPLC), High molecular weight proteins (HPSEC), pH (potentiometry Ph.Eur.), sterility (Ph.Eur.), bacterial endotoxins (Ph.Eur.), particulate matter (visible particle, Ph.Eur.), particulate matter (subvisible particles, Ph.Eur.), antimicrobial preservative content (HPLC), extractable volume (Ph.Eur.), identification of pen-injector (visual), functional test of pen-injector (gravimetry), dose accuracy according to ISO standard 11608-1 (gravimetry).

Analytical methods have been suitably described and all non-compendial analytical procedures, such as HPLC and HPSEC as well as the analytical procedures for sterility and bacterial endotoxins were validated to demonstrate that they are suitable for their intended purpose. The pen-related analytical procedures were adequately described under Section 3.2.P.7 "Container closure system".

Batch analysis data are provided for 10 production batches and 6 pilot batches for the 20 µg strength and 4 production batches and 2 pilot batches for the 10 µg strength. The results presented are within the proposed specification.

Container Closure system

The drug product is filled in a 3 ml colourless glass type I cartridge closed with an aluminium flanged cap with inserted laminated sealing disk (isoprene rubber on external side and bromobutyl rubber on product side) and a bromobutyl rubber plunger stopper. A brief description of the packaging components is given together with their specifications and batch analysis. The glass cartridges and bromobutyl rubber components comply with the relevant requirements of Ph. Eur. 3.2.1 'Glass containers for Pharmaceutical Use' and Ph. Eur. 3.2.9 'Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for freeze-dried Powders.

The glass cartridges are assembled into disposable pen-injectors. A pen-injector is available for each dosage strength (green for 10 µg and purple for 20 µg per 0.2 mL volume administered). The strength of administered dose depends on the concentration of the solution in the cartridge. Apart from color and tactile features, the geometry and function of each pen version is identical and consists of cap, cartridge holder, cartridge (containing lixisenatide solution for injection), body, mechanism and button. None of these components are in direct contact with the drug product. Materials used for the pen-

injector are listed in the dossier together with conformity regulations. Specifications are presented for the assembled pen-injector. These include tests for identification (visual), appearance, functional test and dose accuracy according to ISO 11608-1.

Stability of the product

Stability studies have been performed on three production-scale and 2 pilot-scale batches for the 10 µg strength and on three production-scale batches for the 20 µg strength. The samples were kept in the cartridges and in the assembled pen-injector and were stored under ICH long-term conditions (24 months at 5°C±3°C), accelerated conditions (6 months at 25°C±2°C/60%±5% RH) and stress conditions (1 month at +40°C±2°C/75%±5% RH). Cartridges were always stored horizontally to evaluate compatibility with the closures.

The parameters tested during Appearance (visual), Appearance (clarity and color) (Ph. Eur.), Assay lixisenatide (HPLC), Related impurities/ degradation products (HPLC), High molecular weight proteins (HPSEC), pH (Ph. Eur.), Particulate matter (subvisible particles) (Ph. Eur.), Antimicrobial preservative content (m-cresol) (HPLC), Integrity of container / closure system, Preservative efficacy (Ph. Eur./USP.

The analytical procedures are stability-indicating and are the same as those used for the control of the finished product apart from an additional HPLC method used for degradation products (described and validated).

No significant change was observed under long-term conditions, and all the parameters including preservative efficacy and container closure integrity remained within the specification.

Under accelerated, light exposure and stress conditions, the assay content decreased and the impurities increased but no significant changes are observed in the other parameters tested. Container closure integrity is confirmed after six months storage. The results were within the accepted limits.

In addition in-use stability studies, temperature cycling studies and photostability studies under ICH conditions were carried out on 1 batch of each strength.

In-use stability studies in line with the ICH guideline Q1E were performed on one batch of each strength (initially, after 12 months and after 24 months) and trying to mimic the conditions of use. During the 14-day in-use period, these samples are stored at 30°C±2°C/65%RH±5%RH and tested for appearance, lixisenatide assay, related impurities, high molecular weight proteins, pH, particulate matter and antimicrobial preservative content. The results were found satisfactory.

The photostability study was performed in accordance with ICH.

The results show significant degradation when the drug product is exposed to intense light.

For the cycling studies the cartridges were subjected to a storage cycle of 4 days at 25°C±2°C/60%±5%RH and 3 days at 5°C±3°C. The cartridges are analysed after four repetitive cycles (28 days). Testing is performed for appearance, lixisenatide assay, related impurities, high molecular weight proteins and metacresol assay.

Stability results indicate that temperature cycling does not impact the quality of the drug product.

Stability results confirm the proposed shelf-life (normal and in-use) and the storage conditions as described in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information and development, manufacture and control of lixisenatide- a synthetic peptide containing 44 amino acids and the finished product Lyxumia presented in a pen-injector has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product Lyxumia is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been provided to show there is no viral/TSE safety risk.

2.2.6. Recommendation for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

Pivotal safety studies were performed in accordance with GLP, except for one cardiovascular study in rats and the hERG assay, which was not considered to be of concern to CHMP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Lixisenatide binding to the GLP-1 receptor was studied by displacement of [125I]GLP-1(7-36) amide binding to CHO-1 cells transfected with the human GLP-1 receptor. Lixisenatide had a binding affinity ~4 times greater than native human GLP-1 to GLP-1 receptor (IC50 = 1.43 nmol/l, Ki = 1.33 nmol/l). Lixisenatide showed no relevant activity on a panel of 91 different receptors and ion channels.

In the perfused pancreas isolated from normoglycemic Wistar rats, it was demonstrated that neither native GLP-1 nor lixisenatide induced insulin secretion at physiologic glucose concentrations (5.6 mmol/L). In contrast, when the ambient glucose concentration was increased to hyperglycemic levels (16.5 mmol/L), both lixisenatide and GLP-1 significantly increased pancreatic glucose-stimulated insulin secretion.

Lixisenatide dose-dependently improved oral glucose tolerance in diabetic db/db mice, diabetic ZDF rats and dogs following a single dose administration of lixisenatide.

In mouse and rat diabetes models, chronic treatment with lixisenatide reduced the progressive increase in basal blood glucose and HbA1c seen in control animals. In mice and dogs, lixisenatide was shown to inhibit gastric emptying and subsequent glucose absorption. In mouse and rat models of diabetes, lixisenatide showed a trend towards enhancement of insulin biosynthesis and β-cell proliferation.

Secondary pharmacodynamic studies

In isolated Langendorff-perfused rat hearts with regional ischemia and reperfusion, lixisenatide reduced the development of myocardial infarction. In male ApoE knockout mice (B.129P2-apoe tm1Unc/J) treated by continuous subcutaneous infusion for 16 weeks, lixisenatide reduced atherosclerotic plaque formation by ~30% compared to placebo.

Safety pharmacology programme

Effects on CNS were studied in general behavior (Irwin) studies in rats and mice. In rats 10 micrograms/kg intravenous (IV) resulted in reversible and slight decrease in locomotor activity and body tone. In mice no effects were observed at SC doses up to 2 mg/kg. A slight dose-dependent block of hERG currents was seen with a maximum inhibition of 37.3% at the highest concentration tested (30 micrograms/ml). There were no changes in resting membrane potential or action potential parameters of rabbit Purkinje fibers up to concentrations of 0.37 micrograms/ml. Cardiovascular studies in vivo were conducted in conscious rats and anaesthetised dogs. A limited increase in mean arterial blood pressure was observed in the rat (≥50 micrograms/kg IV), but not in the dog (high dose 10 micrograms/kg IV). Lixisenatide had no relevant effects on the respiratory system in anaesthetised dogs.

2.3.3. Pharmacokinetics

Nonclinical PK studies of lixisenatide were performed in 2 strains of mice, in rats, two strains of rabbits, dogs, and pigs using intravenous (IV), subcutaneous (SC), or intraperitoneal (IP) administration. In almost all of these studies, high doses of lixisenatide were used in order to achieve plasma concentrations in the low nanomolar range that could be detected by the analytical method available at that time, liquid chromatography/mass spectrometry, which is less sensitive than the immunoassay used in TK studies later on. Thus, the PK understanding is mainly based on supra-therapeutic exposure levels.

In all species, lixisenatide was rapidly absorbed following SC or IP administration with maximum plasma concentrations (C_{max}) occurring between 0.25 and 3.75 h after dosing. After SC dosing, the absolute bioavailability was: dogs (~90%), pigs (~70%), db/db mice (36 to 50%), rabbits (>30%), and rats (~3%). The terminal half-lives of lixisenatide ranged between 0.5 and 6.5 h after IV administration in different animal species (mouse, rat, rabbit, dog, and pig).

Lixisenatide was intensively metabolised after 1 h incubation in S9 liver and kidney fractions from humans, dogs, and rabbits. In human S9 fractions, 28 metabolites were detected; all of them were degraded peptide products of lixisenatide.

A sensitive, specific method for lixisenatide (ELISA) revealed no sign of lixisenatide in brain (except the part expected from the amount of plasma in brain), a very low placental transfer (0.1% in rat and < 0.01% to 0.3% in rabbit) and a very low amount of lixisenatide in milk.

2.3.4. Toxicology

Single dose toxicity

In rat and mouse exploratory studies (limit dose testing) single doses of aqueous solutions of lixisenatide up to 500 micrograms/kg IV and SC in mice and 5000 micrograms/kg IV and SC in rats resulted only in transient clinical findings such as lethargy, piloerection and decreased activity.

Repeat dose toxicity

Repeat dose toxicity studies were performed in mice, rats and dogs with durations up to 6 months in rats and 12 months in dogs. There were no important toxicological findings reported in mice or rats. However, in the chronic rat study testicular and epididymal effects appeared to occur in the high dose group with cases of atrophy, spermatid stasis and mineralisation in the testis and oligospermia and aspermia in the epididymis. In dogs, reversible testicular and epididymal toxicities were observed. The applicant proposes that these effects could be due to GLP-1 receptor mediated effects on fluid resorption in the epididymis. Receptor expression analysis in testes and epididymis of rats, dogs and humans revealed that GLP-1R is expressed at least 3.3-fold higher in dogs compared to humans and at least 100-fold compared to rats. These results indicate that dogs may be more susceptible for testicular and epididymal GLP1-R activation and corresponding effects by lixisenatide than rats and, to a lesser extent, also more susceptible than humans.

Genotoxicity

Lixisenatide was negative in a standard battery of genotoxicity tests (Ames test, human lymphocyte chromosome aberration test, mouse bone marrow micronucleus test).

Carcinogenicity

Two-year carcinogenicity studies in mice and rats were performed with dose levels of 40, 200 and 1000 µg/kg BID. In agreement with other GLP-1 receptor agonists, lixisenatide showed proliferative effects on thyroid C-cells in both species. The applicant has performed a number of mechanistic studies showing higher expression of GLP-1 receptor in thyroid tissue from rats compared to human tissue, functional activity in a rat C cell line but not in a human C cell line and GLP-1 receptor mediated calcitonin release in mice.

A statistically significant trend for increase in adenocarcinoma in the endometrium was found in lixisenatide-treated CD-1 mice as compared to control mice.

Reproduction Toxicity

There were no adverse effects on fertility or early embryonic development in the rat at any dose tested.

Embryofetal development toxicity was studied in rats and rabbits. In the rat, there was one fetus with microphthalmia (LD), one fetus with anophthalmia (MD), one fetus with diaphragma hernia (MD) and three fetuses with multiple skeletal malformations (1LD, 1MD, 1HD). In addition there was a dose-dependent retardation of fetal growth and ossification. In rabbits there were five cases of multiple malformations (2LD, 2MD and 1HD). There was also a cardiac ventricular septum defect (HD), and lack of gall bladder (1MD, 2HD). Also in rabbits, there were other findings of skeletal anomalies and retarded ossification. In a second rabbit study with lower doses, multiple skeletal and visceral malformations were seen in one markedly retarded control group fetus. In rats no NOAEL was defined. In rabbits, the second study gave a NOAEL of 2.5 micrograms/kg BID with an AUC of 41.5 ng*h/mL (exposure margin 5.7x)

Pre- and postnatal development toxicity was studied in rats. There was maternal toxicity at all doses with decreased motor activity, piloeretion, decreased body weight and food consumption. There was increased pup mortality at the high dose and lower body weight gain at ≥20 micrograms/kg twice daily. There were two cases of multiple skeletal malformations in animals found death at birth.

Other toxicity studies

An 8-month toxicity study was performed in male juvenile dogs. There were adverse microscopic findings in testis and epididymis at all doses. Testicular and epididymal findings were absent after the recovery period of 2 months. The findings on testicular and epididymal toxicity are similar to those seen in the repeat dose toxicity study in adult dogs.

There was a dose- and time-dependent development of antidrug antibodies following SC administration of lixisenatide to mice, rats and dogs in studies up to 12 months in duration. There were no signs of immune-mediated pathology. While the antibodies did not appear to block the pharmacodynamic effect, the pharmacokinetics was affected with higher exposures.

2.3.5. Ecotoxicity/environmental risk assessment

No environmental risk assessment has been performed since according to the ERA guideline: "Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment." This view is endorsed by CHMP.

2.3.6. Discussion on non-clinical aspects

The primary pharmacodynamics of lixisenatide were found to be consistent with what has been shown with other members of the class.

Safety pharmacology studies did not raise any concerns.

Repeat dose toxicity studies were adequately performed, and substantial exposure margins to clinical exposure were achieved. The only finding of importance was reversible testicular and epididymal toxicities in the dogs. While not considered as a toxicological finding in the study report, in the high dose animals in the chronic rat study there was an increased number of animals with similar testicularand epididymal changes. Similar effects were also seen in a juvenile toxicity study in dogs with no NOAEL. The applicant proposed that these effects could be due to GLP-1 receptor-mediated effects on fluid resorption in the epididymis. Receptor expression analysis in testes and epididymis of rats, dogs and humans revealed that the GLP-1 receptor is expressed at least 3.3-fold higher in dogs compared to humans and at least 100-fold higher compared to rats. These results indicate that dogs may be more susceptible for testicular and epididymal GLP1 receptor activation and corresponding effects by lixisenatide than rats and, to a lesser extent, also more susceptible than humans. A clinical study has been performed which did not show any adverse effects on sperm parameters.

As with other GLP-1 receptor agonists, lixisenatide showed proliferative effects on thyroid C-cells in mice and rats. Data from the applicant give further support for the hypothesis that the C-cell effects are related to activation of GLP-1 receptor on thyroid C-cells and that there is a species-specific difference in sensitivity to this effect. However, this difference may be only quantitative and it cannot be excluded that the effect could have clinical relevance in an individual with a certain genetic predisposition. The conclusion from the assessments of other GLP-1 receptor agonists is therefore equally applicable for lixisenatide and the proposed text in section 5.3 of the SmPC was therefore endorsed by CHMP stating that findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive.

A statistically significant trend for increase in adenocarcinoma of the endometrium was found in lixisenatide-treated CD-1 mice as compared to control mice. The endometrial findings observed during the mouse carcinogenicity study are mentioned under section 5.3 of the SmPC.

Embryofoetal toxicity was studied in rats and rabbits (two studies). Malformations were observed both in the rat study and the first rabbit study, with no NOAEL. Also, in a rat study on pre- and postnatal toxicity, there were pups with skeletal malformations.

The applicant raised two main arguments to consider these malformations as not being related to treatment: The occurrence in historical controls (or in the case of multiple malformations in rabbits in one single foetus in the second rabbit study) and the lack of a dose response relationship. The reference to a historical database can have relevance in evaluating rare findings but in this case with multiple malformed foetuses the finding of a single or a few cases in a data base of several thousand foetuses was considered by CHMP as not sufficient in order to regard the findings as incidental. Concerning the absence of a dose-response relationship it is relevant that lixisenatide is a peptide and adverse events would be expected to be a pharmacological effect, the dose-response curve of which is not easily predictable. It may well be that once there is a pharmacological effect, a further increase in exposure may not increase the risk and therefore the absence of a dose response relationship was also considered as not sufficient to reassure CHMP that these malformations would not being related to treatment with lixisenatide. It is agreed that maternal effects on body weight and food consumption can result in foetal effects, mainly related to growth retardation, and this has also been shown for other members of the class, but without evidence for an increased rate of malformations. Given that such dramatic effects on body weight and food consumption are not observed clinically, the relevance for humans would be minimal. However, the malformations observed in the developmental toxicity studies with lixisenatide were not completely explained by these maternal effects. The applicant has not been able to demonstrate that these malformations are without doubt unrelated to treatment. Therefore, appropriate recommendations have been included in SmPC section 4.6, stating that Lyxumia should not be used during pregnancy and it is not recommended in women of child-bearing potential not using contraception. Furthermore, the findings in the developmental toxicity studies are described in SmPC section 5.3.

2.3.7. Conclusion on the non-clinical aspects

Non-clinical data reveal no special concerns based on the studies of safety pharmacology and toxicology.

As with other GLP-1 receptor agonists, lixisenatide showed proliferative effects on thyroid C-cells in mice and rats. The clinical relevance of the thyroid C cell tumours in rats cannot be excluded. In the clinical development program there is no indication of trends in the incidences of thyroid neoplasms. This will be followed in post-authorisation studies.

In the developmental toxicity studies there were a number of malformations and a relation to treatment cannot be excluded, and therefore, as a precaution, lixisenatide is not recommended in women of child bearing potential not using contraception.

There are no non-clinical objections to the approval of Lyxumia.

2.4. Clinical aspects

2.4.1. Introduction

The assessment of the efficacy and safety of lixisenatide was based on a clinical program, comprising 41 completed or ongoing clinical studies, including 24 Phase 1 studies, 4 Phase 2 studies, and 13 Phase 3 studies.

The proposed indication is based on the results of 6 randomised double-blind, placebo-controlled phase 3 studies and 1 randomised open-label, active-controlled phase 3 study versus exenatide.

The analysis of safety is based on data from 26 of the completed studies, in which 3708 people received at least 1 dose of lixisenatide, including 3343 patients with T2DM and 365 healthy subjects.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1 - Overview of the lixisenatide clinical development program (at primary data cut-off date)

Study	Patients randomized *	Type of control	Lixisenatide treatment combination	Main objectives
Phase 1				
01-016	28	Placebo	Monotherapy	Safety
BEQ11094	90	Uncontrolled	Monotherapy	Pharmacokinetics (bioequivalence)
BDR6864	43	Uncontrolled	Monotherapy	Pharmacokinetics (bioavailability)
BDR10880	43	Uncontrolled	Add-on to insulin glargine	Pharmacokinetics (relative bioavailability and activity in T1DM)
BDR11038	26	Uncontrolled	Add-on to insulin glargine	Pharmacokinetics (relative bioavailability and activity in T1DM)
BDR11540	24	Uncontrolled	Add-on to insulin glargine	Pharmacokinetics (relative bioavailability)
BDR11578	23	Uncontrolled	Add-on to insulin glargine	Pharmacokinetics (relative bioavailability and activity in T1DM)
INT6052	25	Placebo	Monotherapy	Pharmacokinetics (drug interaction with oral contraceptive)
INT6863	15	Placebo	Monotherapy	Pharmacokinetics (drug interaction with acetaminophen)
INT10408	16	Uncontrolled	Monotherapy	Pharmacokinetics (drug interaction with warfarin)
INT10409	36	Uncontrolled	Monotherapy	Pharmacokinetics (drug interaction with atorvastatin)
INT10782	30	Uncontrolled	Monotherapy	Pharmacokinetics (drug interaction with ramipril)
INT10783	24	Uncontrolled	Monotherapy	Pharmacokinetics (drug interaction with digoxin)
PDY10433	22	Placebo	Monotherapy	Pharmacodynamics (first- and second phase insulin release in T2DM)
PDY11431	24	Placebo	Monotherapy	Pharmacodynamics (gallbladder motility)
PDY11824[a]	18 planned	Placebo	Monotherapy	Pharmacodynamics (first- and second phase insulin release in healthy subjects)
PDY11941	18	Placebo	Monotherapy	Pharmacodynamics (response to hypoglycemia)
POP6053	32	No renal impairment	Monotherapy	Pharmacokinetics and safety (renal impairment)
POP11320	22	Uncontrolled	Monotherapy	Pharmacokinetics in Chinese subjects
POP11814	36	Young subjects	Monotherapy	Pharmacokinetics (elderly subjects)
TDR11215[a]	275	Placebo	Monotherapy	Safety (sperm concentration)
TDU10121	68	Placebo	Monotherapy	Pharmacokinetics (prolonged release formulation)
TES6865	91	Placebo and active (moxifloxicin)	Monotherapy	Safety (thorough QTc)

TES11807[a]	260 planned	Placebo and active (moxifloxicin)	Monotherapy	Safety (thorough QTc)
Phase 2				
ACT6011	65	Placebo	Add-on to SU or metformin or SU+metformin	Pharmacodynamics
DRI6012	542	Placebo	Add-on to metformin	Dose response
PDY6797	120	Placebo	Add-on to SU or SU+metformin	Pharmacokinetics, pharmacodynamics and safety
PDY10931	148	Active (liraglutide)	Add-on to metformin	Pharmacodynamics
Phase 3				
EFC6014	680	Placebo	Add-on to metformin	Efficacy and safety
EFC6015	859	Placebo	Add-on to SU or SU+metformin	Efficacy and safety
EFC6016	496	Placebo	Add-on to basal insulin or basal insulin+metformin	Efficacy and safety
EFC6017[a]	484	Placebo	Add-on to pioglitazone or pioglitazone+metformin	Efficacy and safety
EFC6018	361	Placebo	Monotherapy	Efficacy and safety
EFC6019[b]	639	Active (exenatide)	Add-on to metformin	Efficacy and safety
EFC10743	484	Placebo	Add-on to metformin	Efficacy and safety
EFC10780	319	Active (sitagliptin)	Add-on to metformin	Efficacy and safety
EFC10781[a]	446	Placebo	Add-on to insulin glargine and metformin	Efficacy and safety
EFC10887	311	Placebo	Add-on to basal insulin or basal insulin+SU	Efficacy and safety
LTS10888	69	Uncontrolled	Monotherapy	Safety in Japanese patients
EFC11319[a]	6000 planned	Placebo	Add-on to standard of care	Cardiovascular outcomes
EFC11321[a]	380 planned	Placebo	Add-on to metformin or metformin+SU	Efficacy and safety

[a] Ongoing studies at the primary cut-off date (30 April 2011).

2.4.2. Pharmacokinetics

Lixisenatide is a new active substance, and pharmacokinetic studies should thus aim at describing the disposition of the substance, support the chosen dosage regimen and, based on the pharmacokinetic properties of the substance, identify sub-groups of patients in which exposure might be altered, and potential interactions with other medical products. Pharmacokinetic data on lixisenatide was available from 23 studies (17 Phase 1, 4 Phase 2, and 2 Phase 3 studies). Of the phase 1 studies, two evaluated biopharmaceutical issues, three intrinsic factors and six interactions. Moreover, eight human biomaterial studies investigating protein binding, metabolic stability of lixisenatide in S9 liver and kidney fractions and identification of metabolites, the potential for lixisenatide to induce cytochrome P450 (CYP) isozyme activity in human hepatocytes or inhibit CYP isozyme activity in human liver microsomes, and the potential for lixisenatide to inhibit human OCT2 (kidney) and OATP1B1 (liver) uptake transporters were submitted. Population PK modelling was conducted including data from two phase 1, two phase 2 studies and two phase 3 studies. Based on exposure measures from the population PK model, population exposure-response models were developed for plasma glucose. In clinical pharmacology studies, single doses from 5 to 20 micrograms and multiple doses from 20 micrograms once daily to 30 micrograms twice daily, for up to 28 days, were evaluated in healthy subjects. Multiple doses from 5 micrograms once daily to 30 micrograms twice daily were evaluated in subjects with T2DM. Lixisenatide concentration in plasma was determined with a validated enzyme-linked immunosorbent assay (ELISA) using a double-antibody sandwich technique measuring total lixisenatide (i.e., unbound and bound to anti-drug antibodies) concentrations. Pharmacokinetic

parameters in clinical pharmacology studies were calculated by non-compartmental methods. Nonlinear mixed effects modelling was used to evaluate PK/PD and population PK.

Lixisenatide PK is greatly influenced by presence of anti-lixisenatide antibodies. The pharmacokinetics was mainly evaluated in subjects and patients without anti-lixisenatide antibodies.

Absorption

After subcutaneous administration, lixisenatide maximum plasma concentrations are reached within about 1.5 to 2.5 hours. The absolute bioavailability of lixisenatide has not been determined. Extent of absorption is independent of injection site, while rate of absorption is somewhat slower after administration in the thigh than in the arm or abdomen resulting in a slightly delayed t_{max} (change in median from 2 to 2.5 hours), and somewhat lower Cmax (mean ratio 0.86).

The 50 micrograms/ml strength is to be used for administration of the 10 microgram starting dose and the 100 microgram/ml strength for the 20 microgram maintenance dose. The applicant performed a bioequivalence study to compare the rate and extent of absorption of the 50 microgram/ml and 100 microgram/ml lixisenatide solutions as the 100 microgram/ml strength was used in Phase 3 also for administration of the 10 microgram dose. Bioequivalence for AUC_{∞} and C_{max} was demonstrated, while the 90% CI of the AUC_{last} ratio was 0.78-0.89.

Distribution

The binding of lixisenatide to human plasma protein was approximately 55%. Lixisenatide has not been administered intravenously. Hence, volume of distribution is not determined. Apparent volume of distribution (Vz/F) was reported to be around 100 l.

Elimination

The apparent clearance (CL/F) is about 30-40 l/h and the terminal half-life around 3 h. The population analysis indicated that lixisenatide has absorption-limited elimination as the population mean absorption time (MAT) of 2.7 hours was longer than the population mean elimination time (V/CL) of 1.15 hours.

Mass balance or excretion has not been evaluated. This is acceptable as lixisenatide is a polypeptide. Being a polypeptide the elimination is expected to follow that of endogenous peptides with renal filtration followed by tubular reabsorption and subsequent metabolic catabolism. Investigations of non-CYP450 metabolism in renal and hepatic S9 fractions in the absence of NADPH metabolism revealed a large number of metabolites, all being degraded peptide products of lixisenatide. The potential to stimulate the GLP-1 receptor was evaluated for four of the metabolites, and none of the investigated metabolites showed any activity.

Dose proportionality and time dependencies

Lixisenatide displays roughly dose proportional increase in exposure in the dose range 5 to 30 micrograms. Lixisenatide seems to display time independent pharmacokinetics and has no accumulation in subjects with no anti-lixisenatide antibodies.

The inter-individual variability for the PK parameters in antibody-negative subjects was generally moderate (CV was for the most part approximately 30% to 60%). The within-subject variation was estimated to be 27% for $AUC_{0-\infty}$ and 22% for Cmax. In antibody-positive patients the variability in exposure of total lixisenatide is markedly increased.

Special populations

PK data in special populations have been obtained in three specific studies (renal impairment, elderly, Chinese subjects). In addition, PK data in Japanese subjects were obtained in type 2 diabetes mellitus patients. The influence of different demographic factors was also evaluated in the population pharmacokinetic analysis. Between-study comparison suggests similar lixisenatide exposure in T2DM patients and healthy volunteers.

In both healthy volunteers and patients lixisenatide AUC and Cmax are markedly increased, tmax delayed and half-life prolonged in anti-lixisenatide antibody positive patients. This is accompanied by a large increase in inter-individual variability. Due to the design of studies it is difficult to distinguish between the effect of dose level and treatment duration. However, the data suggests that antibodies have a large effect on lixisenatide exposure regardless of dose level. In pre-dose samples collected in phase 3 studies, active lixisenatide concentration was measured by bioassay. The active fraction was considerably lower, 22 compared to 72%, however the active concentration was on average only slightly lower (109 vs 123 pg/ml) in antibody positive than in antibody negative patients. The variability in both active and total concentration and active fraction was very large. There was no correlation between active concentration of lixisenatide and concentration of anti-lixisenatide antibodies and active lixisenatide concentration is similar in different anti-lixisenatide antibody concentration groups and the antibody negative group. Further, there seems to be no correlation between total concentration of lixisenatide and concentration of anti-lixisenatide antibodies. Total lixisenatide concentration was higher in groups with low to median antibody concentration than in the group with the highest antibody concentration.

Given the large influence of anti-lixisenatide antibodies on lixisenatide PK, the pharmacokinetics in special populations were evaluated in subjects and patients without anti-lixisenatide antibodies. Hence, there is no information on potential difference in the influence of intrinsic factors on lixisenatide PK between patients with and without anti-lixisenatide antibodies.

In the initial population PK analysis of phase 1 and 2 data renal function (creatinine clearance) was included as a covariate for renal clearance, body weight for non-renal clearance and V/F and injection in the thigh and Asian race as covariates for relative bioavailability. The predicted effects of body weight, injection in the thigh and Asian race were modest (about 20% higher AUC in a patient weighing 35 kg than one weighing 70 kg, 14% increased bioavailability after administration in the thigh and 32% increased bioavailability in Asian race). Age and gender were not identified as significant covariates affecting lixisenatide clearance. In a revised population PK analysis also including phase 3 data and using another structural model creatinine clearance and dose were found to be significant covariates of CL/F, body weight significant covariate of V/F, and dose significant covariate of MAT.

The influence of renal impairment on lixisenatide pharmacokinetics was evaluated in 32 subjects after administration of a single 5 microgram dose to subjects with normal renal function (creatinine clearance >80 ml/min), mild renal impairment (creatinine clearance 50-80 ml/min), moderate renal impairment (creatinine clearance 30-<50 ml/min) and severe renal impairment but not requiring heamodialysis (creatinine clearance 17-30 ml/min). Renal function was determined based to creatinine clearance calculated using the Cockcroft-Gault formula determined at screening. Subjects with normal renal function were matched for age, BMI, and gender to the renally impaired groups. Lixisenatide exposure is increased in subjects with reduced renal function. Mild renal impairment did not affect the pharmacokinetics of lixisenatide and moderate renal impairment had no effect on Cmax and only a small effect on AUC, about 24% increase. Given the signal of a slight increase in adverse events in mild renal impairment and very limited clinical experience in moderate renal impairment, the SmPC recommends use with caution in patients with moderate renal impairment. In severe renal impairment

Cmax was increased by 29% and AUC by 46%. There is no therapeutic experience in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or end-stage renal disease and therefore, it is not recommended to use lixisenatide in these populations in the SmPC.

The influence of hepatic impairment on lixisenatide pharmacokinetics has not been evaluated. No dose adjustment is needed in patients with hepatic impairment as hepatic dysfunction is not expected to affect the pharmacokinetics of lixisenatide.

Female subjects had in general higher exposure than male subjects. The difference in exposure seems at least partly to be due to differences in weight as AUC was comparable in male and female Chinese subjects with similar weight.

The effect of age on lixisenatide pharmacokinetics was evaluated after administration of a single 20-microgram dose in 18 healthy elderly (65-79 years, mean age 72 years) and 18 young (24-44 years, mean age 33 years) subjects matched for body weight and gender. Cmax and tmax were comparable in both study populations. AUC was increased by 29% and half life prolonged by 57% in the elderly. No dose adjustment is required based on age. The SmPC reflects that clinical experience in patients ≥75 years is limited.

Data from clinical pharmacology studies suggest that there is no clinically relevant difference in exposure between Japanese and Caucasian subjects and that Chinese subjects seem to have an exposure in a similar range.

No PK data in children have been provided.

Pharmacokinetic interaction studies

The potential for lixisenatide to inhibit the CYP isoenzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, and the transport proteins OCT2 and OATP1B1 and to induce CYP1A, CYP2B6, CYP2C9, and CYP3A was evaluated *in vitro*. Based on these data lixisenatide is unlikely to cause drug-drug interactions with CYP450 substrates or substrates of OCT2 and OATP1B1.

In vivo lixisenatide delays gastric emptying and may thereby reduce the extent and rate of absorption of orally administered drugs. The influence on gastric emptying was estimated in T2DM patients by means of a ^{13}C-octanoic acid breath test after a standardised breakfast test meal. Lixisenatide delayed gastric emptying resulting in both an increased lag-time and an increased half-life. The effect was larger for the 20 than the 10 microgram group, but similar between once daily and twice daily dosing. The variability was large and it was difficult to draw firm conclusions, but the data suggested that the effect at the 10-microgram dose may be about 80% of the effect expected at the therapeutic dose of 20 micrograms. This conclusion was further supported by simulations performed to predict the effect of lixisenatide 20 micrograms on paracetamol based on the results obtained from the previous interaction study between lixisenatide 10 micrograms and staggered dosing of paracetamol. The simulated data predicted a decrease in paracetamol Cmax by 22% and a delay in its tmax by 1.75 h with the 20-microgram lixisenatide dose compared to the 10 microgram dose (when lixisenatide was given 1 h before paracetamol).

The influence of lixisenatide on paracetamol (as a marker for gastric emptying), on oral contraceptives (efficacy dependent on threshold concentrations), on drugs commonly prescribed in patients with T2DM (ramipril and atorvastatin) and on drugs with narrow therapeutic window (digoxin and warfarin) were evaluated. Lixisenatide in general showed no or very small effects on AUC of the concomitantly administered drugs, but there was a delay in tmax and a reduction in Cmax, which was dependent on when lixisenatide was administered in relation to the concomitantly administered drug.

The effect of lixisenatide on tmax of co-administered drugs was most pronounced for warfarin, which had a prolonged tmax by 7 hours. For the other co-administered drugs, this effect varied between 1 to 4 hours. The apparent pronounced effect on warfarin tmax is likely to be explained by the study design with scarce sampling around Cmax of the compound and possibly also by the narrower dosage interval between warfarin and lixisenatide. When paracetamol, ethinylestradiol, levonorgestrel, atorvastatin, warfarin and digoxin were administered ½-1 hour after the lixisenatide dose, their respective Cmax was reduced by approximately 20%-50%. Based on the results when paracetamol and oral contraceptives were dosed at different time intervals relative to the lixisenatide dose, it was concluded that these effects (prolonged tmax and reduced Cmax), could be avoided if co-administered drugs were given 1 hour before or 11 hours after lixisenatide. In the SmPC drugs that are dependent on threshold concentrations (such as antibiotics) and gastro-resistant formulations are recommended to be administered 1 h before or 4 h after lixisenatide ingestion.

Lixisenatide, dosed in the morning, unexpectedly increased the AUC and Cmax of atorvastatin, dosed in the evening, by 27% and 66%, respectively. These effects were concluded by the applicant to be of no clinical relevance with no need for dose adjustment of atorvastatin. This conclusion was based on that the increased exposure to atorvastatin dosed in the evening was still in the same range as the exposure to atorvastatin dosed without lixisenatide in the morning. In addition, an analysis of phase III data did not reveal any differences in the report of adverse events between patients with and without co-administration of statins. The reduction in Cmax of ethinylestradiol and levonorgestrel, were in the same range as has been observed for Byetta, and is mentioned in a similar way in the SmPC 4.5.The exposure of ramipril was also affected by lixisenatide with increased AUC (by 21%) and reduced Cmax (by 63%). However, since these parameters were unaffected for the active metabolite (ramiprilat), no dose adjustments are required when co-administering ramipril with lixisenatide.

The SmPC indicates that no dose adjustment is required for atorvastatin, oral contraceptive and ramipril when co administered with lixisenatide.

2.4.3. Pharmacodynamics

Several PD studies have been performed to assess the primary and secondary pharmacology of lixisenatide

Mechanism of action

The physiological GLP-1 receptor agonist, GLP-1, is a hormone (incretin) which is secreted from the L-cells of the gastrointestinal tract following ingestion of a meal. As a class, GLP-1 and its analogs are known to stimulate insulin release from the pancreatic islets (insulinotropic release), suppress glucagon secretion, delay gastric emptying, and reduce body weight.

Primary and Secondary pharmacology

Primary pharmacology

Study **PDY10433** was a placebo-controlled study conducted under euglycaemic clamp conditions in patients with T2DM investigating the insulin response to an intravenous glucose challenge after administration of lixisenatide as a single dose of 20 micrograms.

There was a 6.6-fold increase in first-phase insulin release ($AUC_{0\text{-}10\ min}$) and a 3.0-fold increase in second phase insulin release ($AUC_{10\text{-}120\ min}$). These increases were accompanied by 6.09-fold and 2.08-fold increases in first and second-phase C-peptide releases, respectively. In the same study, there was a reduction in mean glucagon concentrations seen under the euglycaemic clamp conditions during the 2 hours between administration of lixisenatide at a single dose of 20 micrograms and

administration of the intravenous glucose challenge. In contrast, the mean glucagon concentrations increased during this time period after administration of placebo. After administration of the glucose challenge, lixisenatide did not affect glucagon release, as compared to placebo.

The overall trend in all studies was that, compared to placebo, treatment with lixisenatide resulted in decreased postprandial glucagon levels versus baseline at all doses tested with the once daily and twice-daily regimens.

The effect of lixisenatide on gastric emptying rate was investigated by means of a ^{13}C-octanoic acid breath test in **Study ACT6011** in patients with T2DM. Notable increases in the mean half-life and lag-time occurred after treatment with lixisenatide at the 10 and 20 micrograms dose levels in the once daily and twice-daily regimens (eg, increase in half-life of more than 2 hours at the 20 micrograms dose level). The extent of the effect at 10 micrograms of lixisenatide was approximately 80% that observed at 20 micrograms, indicating that lixisenatide delayed gastric emptying at all doses tested.

The effect of lixisenatide on body weight was examined in several phase 2 and 3 studies showing reductions ranging from 1 to 2 kg. Satiety markers were assessed in Study **PDY10931**. This assessment showed some trends toward postprandial decreases in peptide YY_{3-36} (PYY_{3-36}) and oxyntomodulin levels.

Study **PDY11941** was conducted to examine whether the counterregulatory hormone response (glucagon, cortisol, epinephrine, norepinephrine, growth hormone) and hypoglycaemia awareness were preserved during provoked hypoglycaemia in the presence of lixisenatide. There were no indications of an attenuated response to hypoglycaemia.

Secondary pharmacology

Cases of acute pancreatitis have been reported in patients treated with GLP-1 agonists, and it has been discussed whether this could be a potential class effect due to changes in sphincter of Oddi motility subsequent to gastric distension, predisposing patients to gallbladder sludge or gallstone formation and thus pancreatitis. **Study PDY11431** was performed to assess the effect of lixisenatide on gallbladder emptying induced by a continuous infusion of cholecystokinin. Administration of a single 20-microgram dose of lixisenatide in healthy subjects significantly reduced the gallbladder ejection fraction in response to CCK-8 at 30 and 60 minutes compared to placebo. However, no increase of hepatobiliary adverse events was detected in the phase 3 placebo-controlled trials.

Due to potential signals of hypospermatogenesis identified from toxicology studies in dogs (see non-clinical section), a potential for similar changes with lixisenatide in humans was investigated in Study **TDR11215**. The study was conducted in healthy subjects to assess the effect of lixisenatide on sperm concentration, total sperm count, sperm motility and morphology and on reproductive hormones. The results did not show a statistically significant difference compared to placebo with respect to proportion of subjects with at least 50% reduction in sperm concentration, which was supported by secondary endpoints. It is thus unlikely that the findings in dogs are of relevance for humans.

Study **TES6865** was performed with the aim to assess the effect of multiple doses of lixisenatide on QTcF and other ECG parameters (heart rate, QT, QTcB, and QTcN) compared to placebo, with measurement of plasma concentrations of lixisenatide at the times of QTcF assessment.

After multiple administration of lixisenatide at maintenance (20 micrograms once daily) or supratherapeutic (30 micrograms twice daily) doses, there was no mean increase in QTcF from baseline during the time interval of 1 to 5 hours after lixisenatide administration. The mean increase for the moxifloxacin control group versus placebo for this time interval was 9.16 ms. In subjects receiving lixisenatide 20 micrograms once daily or 30 micrograms twice daily, the mean heart rate increased by 1.02 and 4.73 bpm, respectively, from baseline compared to placebo. For both lixisenatide doses, the 1-sided nonadjusted upper limit of the 95% CI of the largest time-matched

mean difference from baseline versus placebo on Day 28 was <10 ms for both QTcF (9.36 ms in the 20 micrograms QD group and 8.58 ms in the 30 micrograms BID group) and QTcN (9.92 ms for the 20 micrograms once daily group and 5.05 ms for the 30 micrograms BID group). No prolonged QTcF, QTcN, or QTcB intervals (>450 ms for males, >470 ms for females), no increases of >60 ms in QTcF, QTcN, or QTcB from baseline were observed for subjects receiving lixisenatide. There was a non significant increase of PR interval compared to moxifloxacin/placebo.

To obtain time-matched baseline measurements to allow detection of differences in diurnal patterns between subjects that would not otherwise be detected by a predose baseline measurement, a second thorough QT/QTc study (TES11807) has been conducted to provide further evidence on the cardiac safety of lixisenatide. This study had a larger sample size (planned with 65 subjects per treatment group) compared to Study TES6865 (planned with 22 subjects per treatment group). In study TES11807, neither 20 micrograms lixisenatide once daily nor 30 micrograms lixisenatide twice daily prolonged the QTcF interval. Transient increases were observed for heart rate and less pronounced ones for PR interval (see further safety section).

Relationship between concentration and response

Lixisenatide reduces fasting plasma glucose concentration over time which could be described by an inhibitory indirect response model. The inter-individual variability of the sensitivity (EC50) in the response to lixisenatide was high. The effect of weight, gender, age and race was investigated but no firm conclusion about covariate effects could be drawn.

The plasma glucose response to a standardised breakfast challenge decreased with increasing exposure of lixisenatide which was described using an Emax model. The effect of weight, gender, age and race was investigated but no firm conclusion about covariate effects could be drawn.

2.4.4. Discussion on clinical pharmacology

Lixisenatide PK is greatly influenced by presence of lixisenatide antibodies. The pharmacokinetics were therefore mainly evaluated in subjects and patients without anti-lixisenatide antibodies. The variability in exposure is markedly increased in antibody-positive subjects. Antibody formation does not affect the active lixisenatide concentration, and would hence from a pharmacokinetic perspective not be expected to affect efficacy. Effects of intrinsic and extrinsic effects were based on evaluation of data in anti-body negative patients only. The effects of intrinsic factors on lixisenatide concentration in antibody-negative subjects are in general modest, with the largest effect observed in severe renal impairment in which use is not recommended. It is not expected that effects of other intrinsic factors on lixisenatide PK would differ to a clinically relevant extent between antibody positive and antibody negative subjects. Therefore, the lack of evaluation of intrinsic effects on active lixisenatide concentration in antibody-positive subjects can be accepted.

The absorption, distribution, metabolism and elimination of lixisenatide have in general been adequately characterised. The extent of absorption is independent of injection site, while rate of absorption is somewhat slower after administration in the thigh than in the arm or abdomen resulting in a slightly delayed tmax (change in median from 2 to 2.5 hours), and somewhat lower Cmax (mean ratio 0.86). The small difference in absorption rate between injections sites is not considered clinically relevant.

The 100 microgram/ml strength was used in Phase 3 also for administration of the 10 microgram dose. In the bioequivalence study comparing rate and extent of absorption after administration of a 10 microgram dose of the 50 microgram/ml and 100 microgram/ml lixisenatide solutions, bioequivalence for AUC_{∞} and C_{max} was demonstrated, while the 90% CI of the AUC_{last} ratio was 0.78-0.89. The 50 microgram/ml strength is used for titration purposes and the slightly lower AUC_{last} is not of safety or

efficacy concern. The deviation from the normal acceptance range is small and as it is not considered to be of any clinical relevance, this deviation in the demonstration of bioequivalence is considered acceptable.

Renal function is the intrinsic covariate affecting lixisenatide exposure the most. The effect of renal function on lixisenatide PK has been evaluated in a dedicated phase I study, as has the effect of age and to some extent race. Apart from renal impairment, the difference between exposures in different sub-groups seems to be small in relation to the large variability in PD. Effects of gender, weight and race seem to be fairly small and are judged not to be clinically relevant. Consequently, although some shortcomings were identified in the population pharmacokinetic analyses evaluating effects of intrinsic factors, further development or qualification of the population PK analysis models is not expected to change the conclusion regarding effects of intrinsic factors.

Renal function is the main factor influencing the pharmacokinetics of lixisenatide, with an observed 24% increase in AUC in moderate renal impairment and 46% in severe renal impairment. Patients with creatinine clearance < 17 ml/min including dialysis patients were not evaluated in this study. A larger effect on lixisenatide exposure is expected in these patients. It is noted that data in the renal impairment study are variable and exposure to a large extent overlapping between renal function groups. The SmPC states that use is not recommended in severe renal impairment (creatinine clearance <30 ml/min) or end stage renal disease, and that Lyxumia should be used with caution in patients with moderate renal impairment (creatinine clearance 30-50 ml/min). Given the large overlap in exposure between renal function groups this is acceptable from a pharmacokinetic perspective.

The influence of hepatic impairment on lixisenatide pharmacokinetics has not been evaluated. This is considered acceptable as lixisenatide is a 44 amino-acid protein with a molecular weight of about 4800 which is expected to be mainly cleared by renal elimination. No dose adjustment is needed in patients with hepatic impairment.

The interaction potential of lixisenatide has in general been well documented. The interaction studies showed that lixisenatide reduced the rate but not the extent of absorption of the concomitantly administered drugs. The delay in the rate of absorption of orally administered medicinal products caused by lixisenatide has led to the recommendation that medicinal products that are particularly dependent on threshold concentrations for efficacy (such as antibiotics) and gastro-resistant formulations should be taken at least 1 h before or 4 h after lixisenatide. Further, medicinal products that have a narrow therapeutic ratio or that require careful clinical monitoring should be followed closely.

As a class, GLP-1 and its analogs are known to stimulate insulin release from the pancreatic islets (insulinotropic release), suppress glucagon secretion, delay gastric emptying, and reduce body weight.

This mechanism of action has been confirmed in the performed PD studies which indicate that there does not seem to be any major differences between the mechanism of lixisenatide compared to other compounds in the class. The counteracting hormone response to hypoglycaemia is not blunted by lixisenatide. There was a reduction of gallbladder ejection fraction which could result in an increased risk of pancreatitis. This event will be monitored in post marketing studies and information is included in the product information. In the submitted QT study, there were no indications of a QT prolonging effect, but a possible effect on the PR interval. The results of a new QT study have been submitted. In this study (Study TES11807), neither 20 microgram lixisenatide once daily nor 30 microgram lixisenatide twice daily did prolong the QTcF interval. Transient increasing effects were observed for heart rate and less pronounced for PR interval.

In dogs, hypospermatogenesis and focal sperm stasis were seen after ≥13-week treatment at high doses and high exposure multiples. A study in healthy males TDR11215 did not show a statistically

significant difference compared to placebo with respect to proportion of subjects with at least 50% reduction in sperm concentration, which was supported by secondary endpoints. It is thus unlikely that the findings in dogs are of relevance for humans.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of lixisenatide has been adequately characterised. Except for severe renal impairment, there is a moderate influence of intrinsic factors on lixisenatide PK. Exposure differences based on age (up to 79 years), weight, race, mild and moderate renal impairment were less than 30%. The interaction potential of lixisenatide has in general been well documented. Lixisenatide delays gastric emptying and may thereby reduce the rate of absorption of orally administered drugs. Lyxumia should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption, require careful clinical monitoring or have a narrow therapeutic ratio.

This mechanism of action has been confirmed in the performed PD studies which indicate that there does not seem to be any major differences between the mechanism of action of lixisenatide compared to other compounds in the class. In the submitted QT study, there were no indications of a QT prolonging effect, but a possible effect on the PR interval. The results of a new QT study have been submitted. In this study (Study TES11807), neither 20 microgram lixisenatide once daily nor 30 microgram lixisenatide twice daily did prolong the QTcF interval. Transient increasing effects were observed for heart rate and less pronounced for PR interval. See further information in the Section Significant Adverse Events in the Safety Section of this report.

2.5. Clinical efficacy

2.5.1. Dose response studies

Based on the results of the phase 2 dose finding studies (in particular study DRI6012), the Applicant came to the conclusion that the optimal benefit/risk ratio was observed with the 20 micrograms once daily dose.

Study DRI6012 was a 13 week, randomised, double-blind, placebo-controlled, parallel-group Phase 2 study assessing the safety, tolerability, and efficacy of lixisenatide administered at several doses once daily or twice daily as an add-on treatment to metformin in patients with T2DM.

Figure 1 Mean change in HbA1c (%) from baseline to endpoint - ITT population

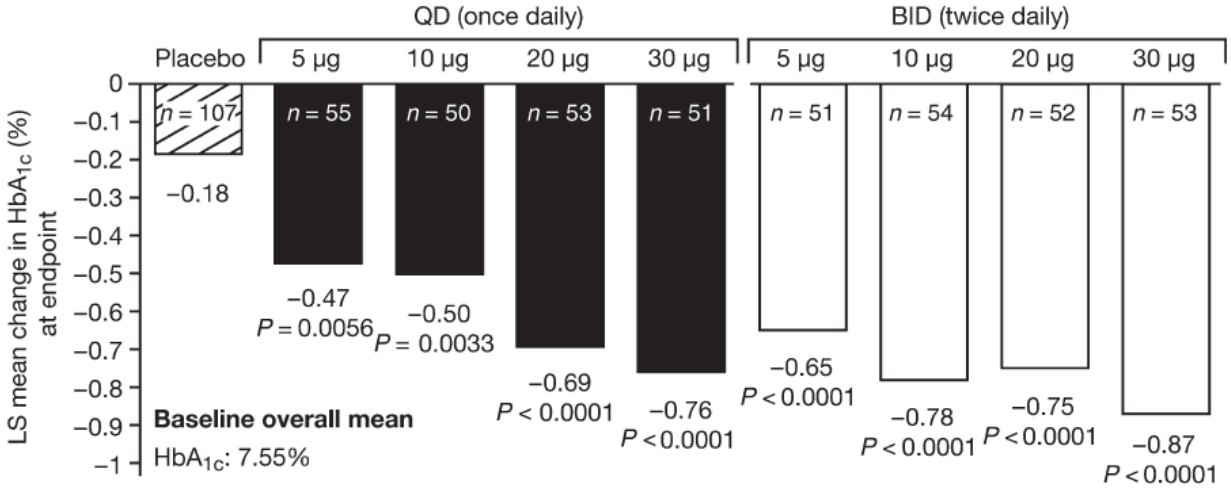


Table 2. Mean change in body weight

Weight (kg)	Placebo (N=108)	AVE0010 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)
Baseline									
N	108	54	50	52	51	51	53	52	53
Mean (SD)	87.66 (13.69)	84.83 (15.56)	90.66 (17.37)	88.93 (17.11)	87.17 (15.19)	86.26 (14.41)	90.02 (16.90)	88.18 (16.76)	87.55 (13.74)
Median	87.40	82.50	88.40	88.05	87.00	84.00	89.80	86.00	88.90
Min : Max	61.0 : 138.8	54.4 : 126.0	59.4 : 147.0	52.4 : 127.0	57.3 : 132.9	56.0 : 129.0	60.5 : 130.0	50.0 : 120.2	58.9 : 120.2
Endpoint									
N	108	54	50	52	51	51	53	52	53
Mean (SD)	86.15 (13.57)	83.31 (15.17)	88.64 (17.63)	86.34 (17.39)	84.15 (15.14)	84.61 (14.29)	88.18 (17.30)	86.00 (16.57)	84.12 (12.95)
Median	85.50	81.40	84.65	87.50	83.50	83.50	87.50	83.00	82.60
Min : Max	61.0 : 139.3	51.3 : 123.0	58.6 : 144.7	49.0 : 125.2	54.0 : 130.2	55.9 : 120.9	61.0 : 131.0	47.0 : 119.9	56.1 : 112.9
Change									
N	108	54	50	52	51	51	53	52	53
Mean (SD)	-1.51 (2.22)	-1.51 (2.65)	-2.02 (2.64)	-2.59 (3.14)	-3.02 (2.86)	-1.65 (2.56)	-1.85 (2.74)	-2.18 (2.15)	-3.43 (2.68)
Median	-1.25	-1.10	-1.75	-2.20	-2.50	-1.60	-1.40	-2.15	-3.70
Min : Max	-10.1 : 6.4	-10.3 : 4.5	-9.7 : 2.2	-11.2 : 3.6	-12.5 : 1.5	-8.1 : 5.0	-11.9 : 2.3	-9.3 : 2.1	-8.6 : 1.2
LS Mean (SE)	-1.94 (0.317)	-2.00 (0.398)	-2.39 (0.418)	-3.01 (0.413)	-3.47 (0.412)	-2.10 (0.406)	-2.21 (0.405)	-2.61 (0.409)	-3.89 (0.414)
LS Mean difference (SE) vs. Placebo	-	-0.05 (0.428)	-0.45 (0.439)	-1.07 (0.433)	-1.53 (0.436)	-0.16 (0.436)	-0.27 (0.431)	-0.67 (0.433)	-1.95 (0.430)
95% CI	-	(-0.896 to 0.786)	(-1.310 to 0.415)	(-1.918 to -0.217)	(-2.384 to -0.671)	(-1.020 to 0.692)	(-1.120 to 0.572)	(-1.521 to 0.181)	(-2.794 to -1.104)
P-value*									
Step down linear trend test									
(QD)		0.9299	0.2962	0.0099	<.0001				
(BID)						0.6920	0.5010	0.1058	<.0001

* Step down linear trend test on change from baseline to endpoint applied the contrasts [-2, -1, 0, 1, 2], [-3, -1, 1, 3], [-1, 0, 1], [-1, 1] from highest to lowest dose, respectively, for BID and QD regimen. Adjusted for baseline value and country.
PGM=AVE0010/DRI6012/CSR_03/BS/PGM_RPT/a_14_2_6_2_eff.sas OUT=OUTPUT/ a_14_2_6_2_eff_WT.rtf (28AUG2008 - 16:34)

Concerning safety, most reports were from the system organ class of Gastrointestinal disorders, with the most frequently reported TEAE being nausea;frequencies ranged from 7.3% (5 micrograms) to 35.2% (30 micrograms) in lixisenatide once daily groups (25.5% with 20 micrograms once daily) and from 7.5% (5 micrograms) to 33.3% (30 micrograms) in lixisenatide twice daily groups (14.3% with 10 micrograms twice daily).

It is agreed that higher doses than 20 micrograms once daily did not contribute much with respect to glucose lowering effect, but were associated with more adverse events. The results indicate that lixisenatide was effective whether it was injected once daily in the morning or once daily in the evening.

2.5.2. Main studies

Pivotal Studies EFC6018, EFC6014, EFC6015, EFC6016, EFC10743, EFC10887, EFC6019

At the primary cut-off date of 30 April 2011, the clinical development program of lixisenatide included 4 phase 2 studies (all completed) and 13 phase 3 studies (9 completed and 4 ongoing).

The placebo controlled phase 3 studies included one monotherapy study (EFC6018) and 5 add-on studies (EFC6014; metformin, EFC6015; SU+/-metformin, EFC6016 ;insulin+/-metformin, EFC10743; metformin, and EFC10887; insulin +/-SU).

One exenatide-controlled study was performed in the add-on to metformin setting (Study EFC6019).

Supportive Study EFC10780

One additional active controlled study vs sitaglitpin (EFC10780) is summarised latter in this report in the Section Supportive Studies.

A ninth phase 3 study was an uncontrolled safety study in Japanese subjects (not included in this report).

Additional Studies EFC6017, EFC10781, EFC11319, EFC11321

The four ongoing studies at the time of MAA were examining lixisenatide as add-on to pioglitazone +/- metformin (EFC6017), as add-on to insulin glargine and metformin +/- TZD (EFC10781), and as add-on to metformin +/- SU (EFC11321). The fourth study is an ongoing cardiovascular outcome study, the results of which are not expected to be available before end of 2014 (EFC11319).

During the procedure, the results of studies EFC10781 and EFC6017 had been submitted.

The following sections describe the pivotal phase 3 studies which were submitted at the start of the procedure.

Methods

All phase 3 studies were parallel-group, controlled, and randomised. A double-blind design was used in 7 out of 8 Phase 3 controlled studies and 3 out of 4 Phase 2 controlled studies. Study EFC6019 was open-label, because a placebo of the active comparator was not available.

Study Participants

All controlled Phase 3 studies were performed worldwide (except Study EFC10887, which was conducted in Asia only). Included patients were adult (ie. >18 years old in most countries), male and female patients with type 2 diabetes, without an upper age limit in pivotal Phase 3 studies. HbA_{1c} was to be between 7 and 10% inclusive and FPG ≤13.9 mmol/L at screening. In the add-on treatment studies, patients were included with a mandatory background antidiabetic medication at a stable dose for at least 2 months (basal insulin) or 3 months (a SU or metformin) before screening.

Treatments

In all Phase 3 studies, except the 12-week Study EFC6018, the maintenance period was composed of a main 24-week controlled treatment period, which was used for the main efficacy analysis. In Studies EFC6014, EFC6015, EFC6016, EFC6019, and EFC10743, the main treatment period was followed by a long-term controlled treatment period, which ended when the last randomised patient completed Week 76 visit.

Objectives

The primary objective of the 7 pivotal Phase 3 studies was to demonstrate the efficacy of lixisenatide on glycemic control as evaluated by the reduction of HbA_{1c} at Week 12 as monotherapy or at Week 24 as add-on treatment. The effect of lixisenatide on body weight and other glucose parameters were assessed as a secondary objective in all studies. In the 5 Phase 3 placebo-controlled studies antibody status (positive or negative) and concentration of anti-lixisenatide antibodies were evaluated.

Participant flow

In total, 3825 patients with T2DM were randomised in the 7 pivotal Phase 3 studies out of which the majority (98.1% to 100.0% depending on the treatment group) was included in the mITT efficacy analysis.

The following numbers of patients were randomised to lixisenatide by background therapy in the mITT population:

- 238 patients to lixisenatide as monotherapy
- 570 patients to lixisenatide as add-on to SU with or without metformin, including 88 patients with SU alone
- 1145 patients to lixisenatide as add-on to metformin alone
- 327 patients to lixisenatide as add-on to basal insulin with or without metformin, including 67 patients with basal insulin alone
- 154 patients to lixisenatide as add-on to basal insulin with or without SU, including 46 with basal insulin alone

Overall in pivotal Phase 3 studies, more than 85% of randomised patients in all treatment groups completed the main treatment period (24 weeks in most studies). In studies lasting at least 76 weeks, the completion rate ranged from 64.7 to 81.4% in the lixisenatide group and from 68.9 to 78.4% in the placebo group.

The main reasons for treatment discontinuation during the main treatment period in the lixisenatide groups were adverse events (mainly gastrointestinal side effects), followed by other reasons. In all Phase 3 placebo-controlled studies, the number of patients discontinuing the investigational product during the main treatment period for lack of efficacy was 0 to 0.9% in the lixisenatide group compared to 0.6 to 2.4% in the placebo group.

Baseline data

Baseline demographic characteristics were generally comparable between treatment groups within each pivotal Phase 3 study. In the mITT population, the majority of all patients was Caucasian: 52.2% in Study EFC6015; 73.0% in Study EFC6018; 77.5% in Study EFC6016; and approximately 90% in "add-on to metformin alone" studies (EFC6014, EFC10743, and EFC6019), in which fewer than 10% of patients were Asian. All patients were Asian (Japan, South Korea, Philippine Islands, and Taiwan) in Study EFC10887, as well as 44.7% (Taiwan, India, Japan, South Korea, Thailand) of patients in Study EFC6015, 22.0% in Study EFC6018, and 16.8% in Study EFC6016. The percentage of black patients ranged from 0 to 4.1%. The proportion of Hispanic patients was 35.7% in Study EFC6014, 30.1% in Study EFC10743, and 45.5% in Study EFC10780.

The gender ratio was generally comparable between groups and across placebo-controlled studies, with a range of 48.5% to 56.9% of female patients.

Median age of the study population ranged from 54 to 59 years across pivotal studies. The majority of patients were between 50 and 65 years of age. The percentages of patients ≥65 to <75 years of age ranged from 8.1% (Study EFC10743, lixisenatide 2-step) to 25.5% (Study EFC10887, placebo) and ≥75 years ranged from 0% (Study EFC10743, lixisenatide) to 5.2% (Study EFC10887, lixisenatide).

The shortest mean duration of diabetes (2.50 years in all patients) was observed in Study EFC6018 and in "add-on to metformin alone" studies (from 4.42 years in Study EFC10780 to 6.75 years in Study EFC6019). Mean known duration of diabetes was more than 9 years in Study EFC6015 (add-on to SU) and more than 12 years in Studies EFC6016 and EFC10887 (add-on to basal insulin).

Patients were generally overweight or obese. Excluding Study EFC10887 conducted only in Asian patients, median BMI at baseline in all patients ranged from 28.94 (Study EFC6015) to 32.62 kg/m² (Study EFC6019).

The population in study EFC10887, entirely performed in Asia, had lower BMI (mean 25.3 kg/m²) and daily insulin doses (mean 24.5 U) than are usually seen in an EU population.

The percentage of patients with baseline microvascular complications was as follows; diabetic retinopathy (placebo: 14.5%, lixisenatide 12.7%), diabetic sensory or motor neuropathy (placebo: 23.7%, lixisenatide 22.8%), diabetic autonomic neuropathy (placebo: 3.6%, lixisenatide 1.9%), and diabetic nephropathy (placebo: 8.5%, lixisenatide 6.2%).

Hypertension and dyslipidemia were the most commonly reported co-morbidities at baseline, approx 66 and 50% of patients, respectively. The proportion of patients with a history of CV event was 10.8% in the lixisenatide group. The majority of the patients were nonsmokers. Approximately 80% of the patients had normal baseline renal function based on their creatinine clearance (mL/min). In lixisenatide-treated patients, 17.2% had mild and 1.3% had moderate renal impairment based on their creatinine clearance (mL/minute). Severe renal impairment at baseline was not observed in any lixisenatide-treated patient.

Studies submitted during the MAA procedure.

Study EFC10781

This study included 446 insulin-naïve patients with T2DM insufficiently controlled with stable doses of metformin ≥ 1.5 g/day or a combination of stable doses of metformin ≥ 1.5 g/day with SUs (to be discontinued at screening) and/or TZDs; and HbA1c ≥7% and ≤10% at screening. All patients were started on insulin glargine on top of met +/- TZD and the dose was titrated to a FPG target between 4.4 and 5.6 mmol/L. Patients whose HbA1c was ≥7% and ≤9%, and mean fasting SMPG calculated from the self measurements over the 7 days prior to Visit 12 was ≤7.8 mmol/L, were randomised to receive placebo or lixisenatide for 24 weeks. Insulin glargine could be further titrated if needed during this part of the study.

The demography and patients' baseline characteristics were generally similar across the 2 randomised treatment groups for the safety population. The median patient age was 57.0 years (56.0 years for lixisenatide and 57.0 years for placebo). The majority of patients were Caucasian (74.4%). Both genders were equally represented. At baseline, 53.8% of patients were obese with a median body mass index (BMI) of 30.71 kg/m^2.

Study EFC6017

The primary aim was to assess the efficacy of lixisenatide on glycemic control in comparison to placebo as an add-on treatment to pioglitazone in type 2 diabetes patients treated with pioglitazone (with or without metformin) over a period of 24 weeks. Patients had T2DM diagnosed at least 1 year before the screening visit; insufficiently controlled with pioglitazone at a stable dose of ≥30 mg/day for at least 3 months prior to screening; HbA_{1c} ≥7% and ≤10% at screening; and, for patients treated with metformin, metformin treatment at a stable dose of ≥1.5 g/day for at least 3 months prior to screening.

The majority of patients (392 patients [81.0%]) were taking metformin at screening, with a similar percentage of patients in each of the treatment groups (80.8% and 81.4% in the lixisenatide and placebo treatment groups, respectively). Patients who completed the main 24-week double-blind period entered a variable double-blind extension period, which ended for all patients approximately at the scheduled date of the Week 76 visit (Visit 25) for the last randomised patient.

Outcomes and estimation

Primary Endpoint; reduction of HbA1c

Mean baseline HbA1c was approximately 8% (7.97 to 8.12%, all groups) in all studies in which lixisenatide was used in monotherapy or add-on to metformin, and ranged from 8.25 to 8.53% in studies in which lixisenatide was used as add-on to SU or basal insulin.

Mean difference in reduction of HbA1c compared to placebo when lixisenatide was used as monotherapy was 0.66%. As add on to metformin the placebo adjusted reduction ranged from 0.37 to 0.49%. The placebo groups in these studies showed reductions of HbA1c of 0.35 and 0.4 %, respectively which is considered as a large reduction considering that mean metformin doses at baseline was approx 2g/day. In further post hoc analyses of patients recruited in Western and Eastern Europe, the mean placebo corrected effect was a reduction of HbA1c of approximately 0.5 %.

Table 3 - Placebo-controlled studies in combination with metformin (24-week results).

	Metformin as background therapy				
	Lixisenatide 20 mcg (N= 160)	Placebo (N= 159)	Lixisenatide 20 mcg		Placebo (N= 170)
			Morning (N= 255)	Evening (N= 255)	
Mean HbA_{1c} (%)					
Baseline	7.99	8.03	8.07	8.07	8.02
LS mean change from baseline	-0.92	-0.42	-0.87	-0.75	-0.38
Patients (%) achieving HbA_{1c} <7.0%	47.4	24.1	43.0	40.6	22.0

In study EFC6015 (add on to SU +/-metformin, 84% of patients on combination), the overall placebo adjusted reduction of HbA1c was 0.74%. The proportion of patients achieving HbA1c <7% was 36.4 % for lixisenatide and 13.5% for placebo.

Two studies in the MAA examined the additive effect of lixisenatide when added to ongoing insulin treatment with or without metformin (study EFC6016, approx 80% of patients on metformin) or SU (study EFC10887, approx 70% of patients on SU). In study EFC6016, the placebo corrected reduction of HbA1c was 0.36% (p=0.0002). The insulin doses changed little, but were reduced somewhat more in the lixisenatide group compared to the placebo group (Table 4).

Study EFC10887 was entirely performed in Asia and the study population differed to some extent compared to what is usually seen in Caucasian patients with respect to BMI and insulin doses. In this study, the placebo adjusted reduction in HbA1c was 0.88%. The insulin doses in these studies changed little in the placebo or lixisenatide groups (Table 4).

Table 4: Placebo-controlled studies in combination with a basal insulin (24-week results)

	Basal insulin as background therapy Alone or in combination with metformin		Basal insulin as background therapy Alone or in combination with a sulphonylurea *	
	Lixisenatide 20 mcg (N= 327)	Placebo (N= 166)	Lixisenatide 20 mcg (N= 154)	Placebo (N= 157)
Mean HbA_{1c} (%)				
Baseline	8.39	8.38	8.53	8.53
LS mean change from baseline	-0.74	-0.38	-0.77	0.11
Patients (%) achieving HbA_{1c} <7.0%	28.3	12.0	35.6	5.2
Mean duration of treatment with basal insulin at baseline (years)	3.06	3.2	2.94	3.01
Mean change in basal insulin dose (U)				
Baseline	53.62	57.65	24.87	24.11
LS mean change from baseline	-5.62	-1.93	-1.39	-0.11

*performed in Asian population

In the active controlled study ECF6019, in which lixisenatide was compared to exenatide, the reduction of HbA1c was -0.96% in the exenatide group compared to -0.79% for lixisenatide (mean difference 0.17%, 95% CI 0.03- 0.297 in the predefined mITT population, upper bound 0.315 in the completer population). During the extension period, the proportions of patients who needed rescue therapy were 19.4 and16.2% in the lixisenatide and exenatide groups, respectively.

Table 5 Mean change in HbA_{1c} from baseline to Week 24 in Study EFC6019 – mITT population

Time point	HbA_{1c} (%)	
	Lixisenatide (N=315)	Exenatide (N=315)
Baseline		
Number of patients with available data	295	297
Mean (SD)	7.97 (0.82)	7.96 (0.77)
Week 24 (LOCF)		
Number of patients with available data	295	297
Mean (SD)	7.17 (0.96)	7.01 (0.88)
Change from baseline to Week 24 (LOCF)		
Number of patients with available data	295	297
Mean (SD)	-0.80 (0.88)	-0.95 (0.87)
LS mean (SE) [a]	-0.79 (0.053)	-0.96 (0.054)
LS mean difference (SE) versus exenatide [a]	0.17 (0.067)	
95% CI	(0.033 to 0.297)	

Main Secondary Endpoints

Table 6- LS mean difference in PPG, FPG, and body weight at Week 24 in the Phase 3 placebo-controlled studies – mITT population

Treatment regimen	Study	Treatment group	PPG (mmol/L)		FPG (mmol/L)		Body Weight (kg)	
			N	LS mean diff [95% CI]	N	LS mean diff [95% CI]	N	LS mean diff [95% CI]
Monotherapy	EFC6018	Placebo	54	-	121	-	116	-
		Lixisenatide 2-step increase	53	-3.86 [-5.375, -2.353]	119	-0.87 [-1.374, -0.361]	117	-0.02 [-0.654, 0.701]
		Lixisenatide 1-step increase	62	-4.82 [-6.287, -3.361]	118	-1.08 [-1.586, -0.577]	115	-0.06 [-0.612, 0.737]
Add-on Metformin alone	EFC6014	Placebo	64	-	170	-	168	-
		Lixisenatide morning	200	-4.51 [-5.652, -3.371]	253	-0.94 [-1.329, -0.559]	248	-0.38 [-0.995, 0.239]
		Lixisenatide evening	-	-	255	-0.56 [-1.944, -0.173]	249	-0.39 [-1.006, 0.230]
	EFC10743	Placebo	-	-	158	-	158	-
		Lixisenatide 2-step increase	-	-	160	-0.67 [-1.035, -0.301]	155	-1.05 [-1.727, -0.371]
		Lixisenatide 1-step increase	-	-	158	-0.65 [-1.019, -0.275]	158	-1.00 [-1.687, -0.317]
	Meta analysis of EFC6014 + EFC10743	Placebo	-	-	328	-	326	-
		Lixisenatide[a]	-	-	826	-0.70 [-0.935, -0.468]	810	-0.68 [-1.083, -0.282]
Add-on SU±Metformin	EFC6015	Placebo	120	-	283	-	278	-
		Lixisenatide	249	-5.98 [-6.912, -5.043]	564	-0.63 [-0.919, -0.346]	554	-0.84 [-1.250, -0.421]
Add-on Basal±Metformin	EFC6016	Placebo	123	-	163	-	161	-
		Lixisenatide	235	-3.81 [-4.699, -2.925]	317	-0.08 [-0.590, 0.430]	311	-1.28 [-1.803, -0.747]
Add-on Basal±SU	EFC10887	Placebo	142	-	157	-	157	-
		Lixisenatide	131	-7.83 [-8.887, -6.769]	148	-0.67 [-1.225, -0.112]	150	-0.43 [-0.925, 0.061]

a Pooled 2 lixisenatide arms within a study and a meta-analysis method on the pooled data of EFC6014 and EFC10743 with the inverse of variance as the weight.
Week 24 value is the last observation carried forward (LOCF) before initiation of rescue therapy on or before Week 24 (Week 12 for EFC6018).
Basal = basal insulin; CI = confidence interval; diff = difference; FPG = fasting plasma glucose; LS mean = least squares mean; mITT = modified intent-to-treat; N = total number of patients with available data;

Overall, the mean difference in body weight compared to placebo was approximately 1 kg. The effect was largest in study EFC6016 (1.3 kg). Concerning plasma glucose parameters the effect on post prandial glucose was in general more pronounced compared to fasting plasma glucose.

In study EFC6019, the mean change in body weight was -3.98 kg and -2.96 kg in the exenatide and lixisenatide groups respectively.

Ancillary analyses

In Phase 3 placebo-controlled studies, there were mean decreases in blood pressure values over time compared to baseline values in both treatment groups during the entire treatment period: mean changes in systolic blood pressure ranged from -0.7 mmHg to -2.1 mmHg in the lixisenatide group and 1.1 mmHg to -1.8 mmHg in the placebo group. For diastolic blood pressure mean changes ranged from -0.6 mmHg to -1.5 mmHg in the lixisenatide group and 0.4 mmHg to -1.6 mmHg in the placebo group.

No relevant mean changes were observed for serum lipids (total cholesterol, HDL-C, low-density lipoprotein cholesterol [LDL-C], and triglycerides) over time compared to baseline values in both treatment groups during the entire treatment period.

Clinical studies with Lyxumia indicate improved beta-cell function as measured by the homeostasis model assessment for beta-cell function (HOMA-β). Restoration of first phase insulin secretion and improved second phase insulin secretion in response to an intravenous bolus of glucose were demonstrated in patients with type 2 diabetes (n=20) after a single dose of Lyxumia.

Maintenance of effect

The long-term efficacy of lixisenatide over at least 76 weeks was evaluated in Studies EFC6014, EFC6015, EFC6016, EFC10743 and EFC6019. A controlled design was maintained until the end of the studies. This analysis was based on the mean (SE) change from baseline at each scheduled visit (HbA1c was measured at Week 36 then every 8 weeks) in patients who had an efficacy measurement at that visit, with no rescue medication being initiated prior to that visit. Mean change in HbA1c from baseline at Week 76 in the lixisenatide groups ranged from -0.70% in Study EFC6014 (evening

injection group) to -0.92% in Study EFC10743 (2-step group). Mean decrease in the placebo groups was also sustained up to Week 76, ranging from -0.30% to -0.64%. In Study EFC6019, the change in HbA_{1c} versus baseline at Week 76 was -0.86% in the lixisenatide group and -1.19% in the exenatide group. Concerning body weight, mean body weight remained relatively stable over 76 weeks or continued to decrease slightly in all studies. No further relevant decrease was observed after Week 24 in most of the studies.

Summary of main studies

The following tables summarise the efficacy results from the main (pivotal) studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7 - Summary of main efficacy endpoints in Study EFC6014

Title: A randomised, double-blind, placebo-controlled, parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of AVE0010 on top of metformin in patients with type 2 diabetes not adequately controlled with metformin			
Study identifier	EFC6014		
Design	Multinational, randomised, double-blind, 4-arm, unbalanced design, parallel-group		
	Duration of main treatment phase: Duration of run-in phase: Total duration of treatment:		24 weeks 1 week ≥76 weeks
Hypothesis	Superiority		
Treatments groups 680 patients randomised	Lixisenatide morning		2-step dose increase (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) 255 patients randomized
	Lixisenatide evening		2-step dose increase (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) 255 patients randomized
	Placebo morning		2-step dose increase 85 patients randomized
	Placebo evening		2-step dose increase 85 patients randomized
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from baseline in HbA_{1c} to Week 24

	Key secondary endpoints	2-hour PPG (mmol/L)	Change from baseline in 2-hour postprandial plasma glucose (PPG) to Week 24
		FPG (mmol/L)	Change from baseline in Fasting plasma glucose (FPG) to Week 24
		Body weight (kg)	Change from baseline in body weight to Week 24
		HOMA-β	Change from baseline in β-cell function assessed by homeostasis model assessment (HOMA)- β to Week 24
		Patients (%) requiring rescue therapy	Percentage of patients requiring rescue therapy during the 24-week period
		FPI (pmol/L)	Change from baseline in Fasting plasma insulin (FPI) to Week 24
Database lock	06 April 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	modified intent-to-treat (mITT) population - 24 weeks from baseline			
Descriptive statistics and estimate variability	Treatment group	Placebo	Lixisenatide morning	Lixisenatide evening
	Number of patients	170	255	255
	HbA_{1c} change from baseline: LS Mean (SE)	-0.38 (0.075)	-0.87 (0.065)	-0.75 (0.066)
	2-hour PPG change from baseline: LS Mean (SE)	-1.41 (0.588) [a]	-5.92 (0.415)	-
	FPG change from baseline: LS Mean (SE)	-0.25 (0.166)	-1.19 (0.145)	-0.81 (0.146)
	Body weight change from baseline: LS Mean (SE)	-1.64 (0.269)	-2.01 (0.234)	-2.02 (0.236)
	HOMA-β change from baseline: LS Mean (SE)	-4.16 (2.823)	7.96 (2.450)	4.80 (2.486)
	FPI change from baseline: LS Mean (SE)	-6.23 (3.254)	-5.09 (2.812)	-1.88 (2.862)
	Patients requiring rescue therapy: n (%)	18 (10.6)	7 (2.7)	10 (3.9)
Effect estimate per comparison	Primary endpoint	Comparison groups	Lixisenatide morning versus Placebo	Lixisenatide evening versus Placebo
	HbA_{1c}	LS Mean difference	-0.48	-0.37
		95% CI	-0.657 to -0.312	-0.540 to -0.193
		P-value	<0.0001	<0.0001

	Secondary endpoints	Comparison groups	Lixisenatide morning versus Placebo	Lixisenatide evening versus Placebo
	2-hour PPG	LS Mean difference	-4.51	-
		95% CI	-5.652 to -3.371	-
		P-value	<0.0001	-
	FPG	LS Mean difference	-0.94	-0.56
		95% CI	-1.329 to -0.559	-0.944 to -0.173
		P-value	<0.0001	0.0046
	Body weight	LS Mean difference	-0.38	-0.39
		95% CI	-0.995 to 0.239	-1.006 to 0.230
		P-value	0.2293	0.2181
	HOMA-β [b]	LS Mean difference	12.12	8.96
		95% CI	5.685 to 18.559	2.450 to 15.477
		P-value	-	-
	Rescue therapy [b]	P-value	0.0007	0.0063
	FPI [b]	LS Mean difference	1.14	4.35
		95% CI	-6.275 to 8.561	-3.121 to 11.826
		P-value	-	-
Notes	[a] Placebo morning only, n=85 patients [b] per step-down procedure, analyses considered exploratory			

Table 8 - Summary of main efficacy endpoints in Study EFC6015

Title: A randomised, double-blind, placebo-controlled, 2-arm parallel-group, multicenter, 24-week study followed by an extension assessing the efficacy and safety of AVE0010 on top of a sulfonylurea in patients with type 2 diabetes not adequately controlled with sulfonylurea			
Study identifier	EFC6015		
Design	Multinational, randomised, double-blind, 2-arm, unbalanced design, parallel-group		
	Duration of main treatment phase: Duration of run-in phase: Total duration of treatment:		24 weeks 1 week ≥ 76 weeks
Hypothesis	Superiority		
Treatments groups 859 patients randomised	Lixisenatide		2-step dose increase (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg) 573 patients randomized
	Placebo		2-step dose increase 286 patients randomized
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from baseline in HbA_{1c} to Week 24
	Key secondary endpoints	2-hour PPG (mmol/L) [a]	Change from baseline in 2-hour postprandial plasma glucose (PPG) to Week 24
		FPG (mmol/L)	Change from baseline in Fasting plasma glucose (FPG) to Week 24
		Body weight (kg)	Change from baseline in body weight to Week 24
		HOMA-β	Change from baseline in β-cell function assessed by homeostasis model assessment (HOMA)- β to Week 24
		Patients (%) requiring rescue therapy	Percentage of patients requiring rescue therapy during the 24-week period
Database lock	22 February 2011		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	modified intent-to-treat (mITT) population - 24 weeks from baseline		
Descriptive statistics and estimate variability	Treatment group	Placebo	Lixisenatide
	Number of patients	286	570
	HbA_{1c} change from baseline: LS Mean (SE)	-0.10 (0.071)	-0.85 (0.061)
	2-hour PPG change from baseline: LS Mean (SE) [a]	-0.21 (0.489)	-6.19 (0.408)
	FPG change from baseline: LS Mean (SE)	-0.36 (0.161)	-0.99 (0.139)
	Body weight change from baseline: LS Mean (SE)	-0.93 (0.234)	-1.76 (0.202)

	HOMA-β change from baseline: LS Mean (SE)	6.63 (5.663)	4.83 (4.686)
	Patients requiring rescue therapy: n (%)	36 (12.6)	23 (4.0)
Effect estimate per comparison	Primary endpoint	Comparison groups	Lixisenatide versus Placebo
	HbA_{1c}	LS Mean difference	-0.74
		95% CI	-0.867 to -0.621
		P-value	<0.0001
	Secondary endpoints	Comparison groups	Lixisenatide versus Placebo
	2-hour PPG [a]	LS Mean difference	-5.98
		95% CI	-6.912 to -5.043
		P-value	<0.0001
	FPG	LS Mean difference	-0.63
		95% CI	-0.919 to -0.346
		P-value	<0.0001
	Body weight	LS Mean difference	-0.84
		95% CI	-1.250 to -0.421
		P-value	<0.0001
	HOMA-β	LS Mean difference	-1.80
		95% CI	-12.424 to 8.819
		P-value	0.7387
	Rescue therapy [b]	P-value	<0.0001
Notes	[a] 2-hour PPG was performed in selected sites (n=120 patients in the placebo group and n=249 in the lixisenatide group) [b] per step-down procedure, analyses considered exploratory		

Table 9 - Summary of main efficacy endpoints in Study EFC6016

Title: A randomised, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of AVE0010 in patients with Type 2 diabetes insufficiently controlled with basal insulin				
Study identifier	EFC6016			
Design	Multinational, randomised, double-blind, 2-arm, unbalanced design, parallel-group			
	Duration of main treatment phase: Duration of run-in phase: Total duration of treatment:		24 weeks 1 week ≥76 weeks	
Hypothesis	Superiority			
Treatments groups 496 patients randomised	Lixisenatide		2-step dose increase (10 µg SC QD injections for 1 week, then 15 µg QD injections for 1 week followed by the maintenance dose of 20 µg QD) 329 patients randomized	
	Placebo		2-step dose increase 167 patients randomized	
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from baseline in HbA_{1c} to Week 24	
	Key secondary endpoints	2-hour PPG (mmol/L)	Change from baseline in 2-hour postprandial plasma glucose (PPG) to Week 24	
		7-point SMPG (mmol/L)	Change from baseline in average 7-point self-monitored plasma glucose (SMPG) to Week 24	
		FPG (mmol/L)	Change from baseline in Fasting plasma glucose (FPG) to Week 24	
		Body weight (kg)	Change from baseline in body weight to Week 24	
		Patients (%) requiring rescue therapy	Percentage of patients requiring rescue therapy during the 24-week period	
Database lock	11 March 2011			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	modified intent-to-treat (mITT) population - 24 weeks from baseline			
Descriptive statistics and estimate variability	Treatment group		Placebo	Lixisenatide
	Number of patients		166	327
	HbA_{1c} change from baseline: LS Mean (SE)		-0.38 (0.107)	-0.74 (0.090)
	2-hour PPG change from baseline: LS Mean (SE)		-1.72 (0.543)	-5.54 (0.468)
	7-point SMPG change from baseline: LS Mean (SE)		-0.61 (0.238)	-1.49 (0.201)

	FPG change from baseline: LS Mean (SE)	-0.55 (0.281)	-0.63 (0.233)
	Body weight change from baseline: LS Mean (SE)	-0.52 (0.293)	-1.80 (0.246)
	Patients requiring rescue therapy: n (%)	12 (7.2)	19 (5.8)
Effect estimate per comparison	Primary endpoint	Comparison groups	Lixisenatide versus Placebo
	HbA_{1c}	LS Mean difference	-0.36
		95% CI	-0.550 to -0.174
		P-value	0.0002
	Secondary endpoints	Comparison groups	Lixisenatide versus Placebo
	2-hour PPG	LS Mean difference	-3.81
		95% CI	-4.699 to -2.925
		P-value	<0.0001
	7-point SMPG	LS Mean difference	-0.88
		95% CI	-1.312 to -0.449
		P-value	<0.0001
	FPG	LS Mean difference	-0.08
		95% CI	-0.590 to 0.430
		P-value	0.7579
	Body weight [a]	LS Mean difference	-1.28
		95% CI	-1.803 to -0.747
		P-value	-
	Rescue therapy [a]	P-value	0.5398
Notes	[a] per step-down procedure, analyses considered exploratory		

Table 10 - Summary of main efficacy endpoints in Study EFC6018

Title: A randomised, double-blind, placebo-controlled, parallel-group, multicenter 12-week study assessing the efficacy and safety of AVE0010 in patients with type 2 diabetes not treated with antidiabetic agents					
Study identifier	EFC6018				
Design	Multinational, randomised, double-blind, 4-arm, unbalanced design, parallel-group				
	Duration of main treatment phase:		12 weeks		
	Duration of run-in phase:		1 week		
Hypothesis	Superiority				
Treatments groups 361 patients randomised	Lixisenatide 2-step		2-step dose increase (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) 120 patients randomised		
	Lixisenatide 1-step		1-step dose increase (10 µg for 2 weeks, then maintenance dose of 20 µg QD) 119 patients randomised		
	Placebo 2-step		2-step dose increase 61 patients randomised		
	Placebo 1-step		1-step dose increase 61patients randomised		
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from baseline in HbA_{1c} to Week 12		
	Key secondary endpoints	2-hour PPG (mmol/L) [a]	Change from baseline in 2-hour postprandial plasma glucose (PPG) to Week 12		
		Body weight (kg)	Change from baseline in body weight to Week 12		
		FPG (mmol/L)	Change from baseline in Fasting plasma glucose (FPG) to Week 12		
		Patients (%) requiring rescue therapy	Percentage of patients requiring rescue therapy during the 12-week period		
Database lock	29 January 2010				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	modified intent-to-treat (mITT) population - 12 weeks from baseline				
Descriptive statistics and estimate variability	Treatment group		Placebo	Lixisenatide 2-step	Lixisenatide 1-step
	Number of patients		121	120	118
	HbA_{1c} change from baseline: LS Mean (SE)		-0.19 (0.121)	-0.73 (0.116)	-0.85 (0.119)
	2-hour PPG change from baseline: LS Mean (SE) [a]		-0.65 (0.563)	-4.51 (0.572)	-5.47 (0.549)
	Body weight change from baseline: LS Mean (SE)		-1.98 (0.341)	-1.96 (0.326)	-1.92 (0.338)

	FPG change from baseline: LS Mean (SE)	0.19 (0.255)	-0.68 (0.247)	-0.89 (0.254)
	Patients requiring rescue therapy: n (%)	3 (2.5)	2 (1.7)	1 (0.8)
Effect estimate per comparison	Primary endpoint	Comparison groups	Lixisenatide 2-step versus Placebo	Lixisenatide 1-step versus Placebo
	HbA_{1c}	LS Mean difference	-0.54	-0.66
		95% CI	-0.785 to -0.300	-0.903 to -0.423
		P-value	<0.0001	<0.0001
	Secondary endpoints	Comparison groups	Lixisenatide 2-step versus Placebo	Lixisenatide 1-step versus Placebo
	2-hour PPG [a]	LS Mean difference	-3.86	-4.82
		95% CI	-5.375 to -2.353	-6.287 to -3.361
		P-value	<0.0001	<0.0001
	Body weight	LS Mean difference	0.02	0.06
		95% CI	-0.654 to 0.701	-0.612 to 0.737
		P-value	0.9462	0.8549
	FPG [b]	LS Mean difference	-0.87	-1.08
		95% CI	-1.374 to -0.361	-1.586 to -0.577
		P-value	-	-
	Rescue therapy [b]	P-value	0.6518	0.3260
Notes	[a] 2-hour PPG was performed in selected sites (n=62 in the placebo group, n=60 in the lixisenatide 2-step group, and n=65 in the lixisenatide 1-step group) [b] per step-down procedure, analyses considered exploratory			

Table 11 - Summary of main efficacy endpoints in Study EFC6019

Title: A randomised, open-label, active-controlled, 2-arm parallel-group, multicenter, 24-week study followed by an extension assessing the efficacy and safety of AVE0010 versus exenatide on top of metformin in patients with type 2 diabetes not adequately controlled with metformin			
Study identifier	EFC6019		
Design	Multinational, randomised, open-label, 2-arm, parallel-group		
	Duration of main treatment phase: Duration of run-in phase: Total duration of treatment:		24 weeks not applicable ≥76 weeks
Hypothesis	Non-inferiority		
Treatments groups 639 patients randomised (includes 5 patients excluded from all analyses due to a significant noncompliance with the protocol)	Lixisenatide		2-step dose increase (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) 318 patients randomised
	Exenatide		1-step dose increase (5 µg BID for 4 weeks, and maintenance dose of 10 µg BID) 316 patients randomised
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from baseline in HbA_{1c} to Week 24
	Selected secondary endpoints	FPG (mmol/L)	Change from baseline in fasting plasma glucose (FPG) to Week 24
		Body weight (kg)	Change from baseline in body weight to Week 24
		Patients (%) requiring rescue therapy	Percentage of patients requiring rescue therapy during the 24-week period
Database lock	13 December 2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	modified intent-to-treat (mITT) population - 24 weeks from baseline		
Descriptive statistics and estimate variability	Treatment group	Lixisenatide	Exenatide
	Number of patients	315	315
	HbA_{1c} change from baseline: LS Mean (SE)	-0.79 (0.053)	-0.96 (0.054)
	FPG change from baseline: LS Mean (SE)	-1.22 (0.116)	-1.45 (0.119)
	Body weight change from baseline: LS Mean (SE)	-2.96 (0.231)	-3.98 (0.232)
	Patients requiring rescue therapy: n (%)	7 (2.2)	12 (3.8)

Effect estimate per comparison	Primary endpoint	Comparison groups	Lixisenatide versus Exenatide
	HbA_{1c}	LS Mean difference	0.17
		95% CI	0.033 to 0.297
	Secondary endpoints	Comparison groups	Lixisenatide versus Exenatide
	FPG [a]	LS Mean difference	0.23
		95% CI	-0.052 to 0.522
	Body weight [a]	LS Mean difference	1.02
		95% CI	0.456 to 1.581
	Rescue therapy [a]	Risk difference	-1.6
		95% CI	-4.41 to 1.16
Notes	[a] No formal interferential testing		

Table 12 - Summary of main efficacy endpoints in Study EFC10743

Title: A randomised, double-blind, placebo-controlled, parallel-group, multicenter, 24-week study followed by an extension assessing the efficacy and safety of AVE0010 in 2 titration regimens on top of metformin in patients with type 2 diabetes not adequately controlled with metformin					
Study identifier	EFC10743				
Design	Multinational, randomised, double-blind, 4-arm, unbalanced design, parallel-group				
	Duration of main treatment phase: Duration of run-in phase: Total duration of treatment:		24 weeks 1 week ≥76 weeks		
Hypothesis	Superiority				
Treatments groups 484 patients randomised	Lixisenatide 1-step		1-step dose increase (10 µg for 2 weeks, then maintenance dose of 20 µg QD) 161 patients randomised		
	Lixisenatide 2-step		2-step dose increase (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) 161 patients randomised		
	Placebo 1-step		1-step dose increase 82 patients randomised		
	Placebo 2-step		2-step dose increase 80 patients randomized		
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from baseline in HbA_{1c} to Week 24		
	Key secondary endpoints	FPG (mmol/L)	Change from baseline in Fasting plasma glucose (FPG) to Week 24		
		Body weight (kg)	Change from baseline in body weight to Week 24		
		Patients (%) requiring rescue therapy	Percentage of patients requiring rescue therapy during the 24-week period		
Database lock	25 February 2011				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	modified intent-to-treat (mITT) population - 24 weeks from baseline				
Descriptive statistics and estimate variability	Treatment group		Placebo	Lixisenatide 2-step	Lixisenatide 1-step
	Number of patients		159	160	160
	HbA_{1c} change from baseline: LS Mean (SE)		-0.42 (0.099)	-0.83 (0.099)	-0.92 (0.101)
	FPG change from baseline: LS Mean (SE)		0.11 (0.209)	-0.56 (0.208)	-0.53 (0.212)
	Body weight change from baseline: LS Mean (SE)		-1.63 (0.385)	-2.68 (0.385)	-2.63 (0.389)

	Patients requiring rescue therapy: n (%)	7 (4.4)	5 (3.1)	2 (1.3)
Effect estimate per comparison	Primary endpoint	Comparison groups	Lixisenatide 2-step versus Placebo	Lixisenatide 1-step versus Placebo
	HbA_{1c}	LS Mean difference	-0.41	-0.49
		95% CI	-0.583 to -0.232	-0.670 to -0.317
		P-value	<0.0001	<0.0001
	Secondary endpoints	Comparison groups	Lixisenatide 2-step versus Placebo	Lixisenatide 1-step versus Placebo
	FPG	LS Mean difference	-0.67	-0.65
		95% CI	-1.035 to -0.301	-1.019 to -0.275
		P-value	0.0004	0.0007
	Body weight	LS Mean difference	-1.05	-1.00
		95% CI	-1.727 to -0.371	-1.687 to -0.317
		P-value	0.0025	0.0042
	Rescue therapy	P-value	0.5499	0.0905

Table 13 - Summary of main efficacy endpoints in Study EFC10887

Title: A randomised, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week treatment period assessing the efficacy and safety of AVE0010 in patients with Type 2 diabetes insufficiently controlled with basal insulin with or without sulfonylurea				
Study identifier	EFC10887			
Design	Multinational (Asia), randomised, double-blind, 2-arm, parallel-group			
	Duration of main treatment phase: Duration of run-in phase:		24 weeks 1 week	
Hypothesis	Superiority			
Treatments groups 311 patients randomised	Lixisenatide		2-step dose increase (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) 154 patients randomised	
	Placebo		2-step dose increase 157 patients randomised	
Endpoints and definitions	Primary endpoint	HbA_{1c} (%)	Change from baseline in HbA_{1c} to Week 24	
	Key secondary endpoints	2-hour PPG (mmol/L)	Change from baseline in 2-hour postprandial plasma glucose (PPG) to Week 24	
		Body weight (kg)	Change from baseline in body weight to Week 24	
		7-point SMPG (mmol/L)	Change from baseline in average 7-point self-monitored plasma glucose (SMPG) to Week 24	
		FPG (mmol/L)	Change from baseline in Fasting plasma glucose (FPG) to Week 24	
		Patients (%) requiring rescue therapy	Percentage of patients requiring rescue therapy during the 24-week period	
Database lock	16 July 2010			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	modified intent-to-treat (mITT) population - 24 weeks from baseline			
Descriptive statistics and estimate variability	Treatment group		Placebo	Lixisenatide
	Number of patients		157	154
	HbA_{1c} change from baseline: LS Mean (SE)		0.11 (0.131)	-0.77 (0.137)
	2-hour PPG change from baseline: LS Mean (SE)		-0.14 (0.563)	-7.96 (0.598)
	Body weight change from baseline: LS Mean (SE)		0.06 (0.271)	-0.38 (0.284)
	7-point SMPG change from baseline: LS Mean (SE)		-0.56 (0.271)	-1.91 (0.272)

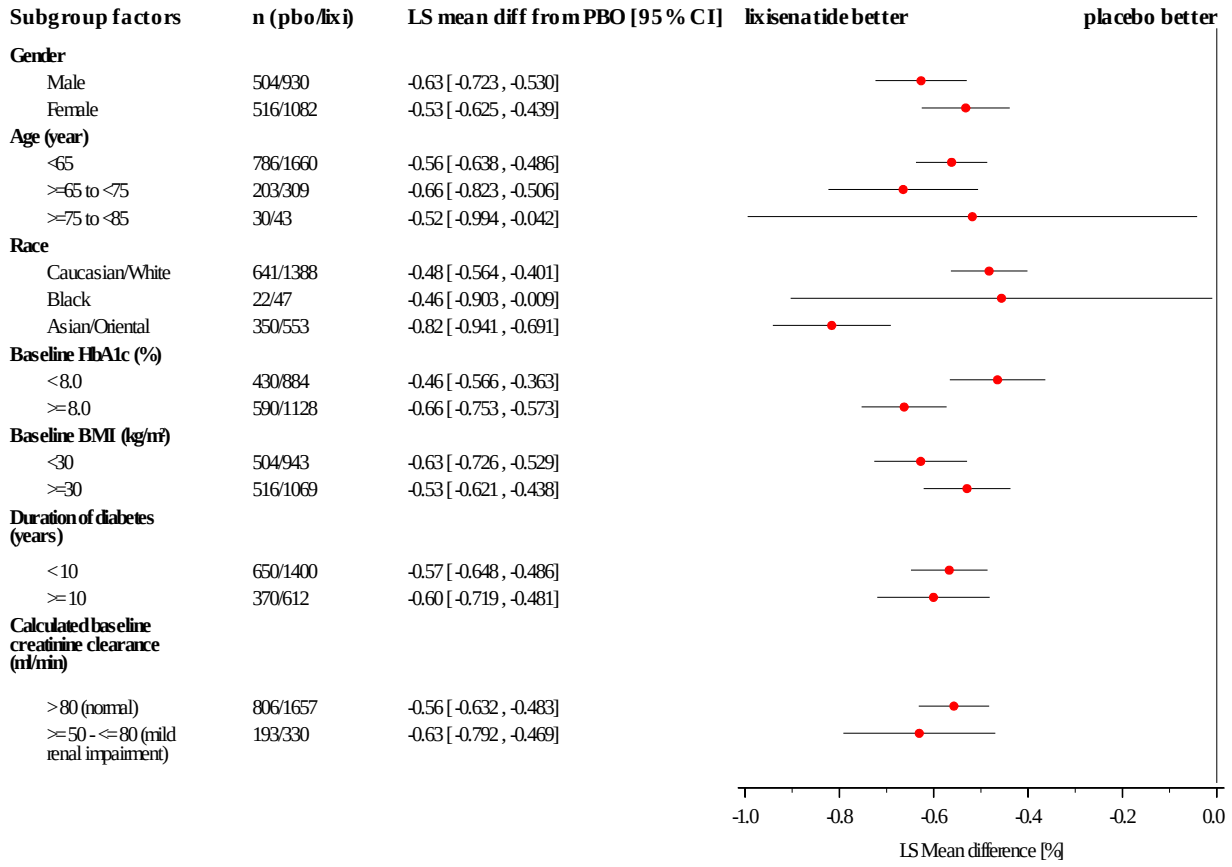
	FPG change from baseline: LS Mean (SE)	0.25 (0.302)	-0.42 (0.314)
	Patients requiring rescue therapy: n (%)	5 (3.2)	2 (1.3)
Effect estimate per comparison	Primary endpoint	Comparison groups	Lixisenatide versus Placebo
	HbA_{1c}	LS Mean difference	-0.88
		95% CI	-1.116 to -0.650
		P-value	<0.0001
	Secondary endpoints	Comparison groups	Lixisenatide versus Placebo
	2-hour PPG	LS Mean difference	-7.83
		95% CI	-8.887 to -6.769
		P-value	<0.0001
	Body weight	LS Mean difference	-0.43
		95% CI	-0.925 to 0.061
		P-value	0.0857
	7-point SMPG [a]	LS Mean difference	-1.35
		95% CI	-1.843 to -0.861
		P-value	-
	FPG [a]	LS Mean difference	-0.67
		95% CI	-1.225 to -0.112
		P-value	-
	Rescue therapy [a]	P-value	0.2564
Notes	[a] per step-down procedure, analyses considered exploratory		

Analysis performed across trials (pooled analyses and meta-analysis)

Clinical studies in special populations

Apart from an indication of a more pronounced effect in Asian compared to Caucasian patients, no striking differences between subgroups have been identified. The number of patients above 75 years of age is limited (N=56). As expected, the effect was more pronounced in patients with high baseline HbA1c.

Figure 2 - Forest plot of LS mean difference between lixisenatide and placebo for change in HbA_{1c} (%) from baseline to Week 24 (Week 12 for EFC6018) by baseline factors across 6 placebo-controlled studies – mITT population



Anti-lixisenatide antibody status was examined in combined data from Studies EFC6015, EFC6016, EFC10743, and EFC10887. At the end of the main treatment period (Week 24), anti-lixisenatide antibody status was assessed as antibody-positive for 69.4% of evaluable patients. For those with high antibody concentrations (group 4, table 14), the mean HbA1c reducing effect was attenuated. However, as no correlation between antibody concentration categories and change in HbA_{1c} was seen, antibody status cannot be used for prediction of the glucose-lowering effect of lixisenatide. These findings are very similar to what has previously been seen for exenatide.

Table 14- Meta-analysis of change in HbA_{1c} (%) from baseline to Week 24 by anti-lixisenatide antibody status and concentration across studies - mITT population

	Lixisenatide			
	n/N (%)	**LS Mean[b]**	**SE[b]**	**95% C.I.[b]**
Anti-lixisenatide antibody status[a]				
Positive	693/998 (69.4%)	-0.81	0.051	(-0.914 to -0.714)
Negative	305/998 (30.6%)	-0.83	0.065	(-0.962 to -0.708)

	Lixisenatide			
	n/N (%)	**LS Mean[b]**	**SE[b]**	**95% C.I.[b]**
Anti-lixisenatide antibody concentration[c]				
Not measured (antibody negative)	305/986[d] (30.9%)			
<LLOQ	477/986 (48.4%)	-0.88	0.054	(-0.989 to -0.778)
Total antibody negative or <LLOQ	782/986[d] (79.3%)	-0.86	0.048	(-0.956 to -0.766)
≥ LLOQ	204/986 (20.7%)	-0.51	0.073	(-0.656 to -0.370)
Group 1	51/986 (5.2%)	-0.75	0.130	(-1.000 to -0.491)
Group 2	52/986 (5.3%)	-0.46	0.126	(-0.708 to -0.215)
Group 3	50/986 (5.1%)	-0.38	0.125	(-0.630 to -0.140)
Group 4	51/986 (5.2%)	-0.18	0.128	(-0.428 to 0.075)

(Group 1: ≥LLOQ to <7.72 nmol/L, Group 2: ≥7.72 nmol/L to ≤15.50 nmol/L, Group 3:>15.50 nmol/L to ≤46.80 nmol/L and Group 4: >46.80 nmol/L).

Supportive studies

Study EFC10780 was a randomised, double-blind, double-dummy, active controlled, 2-arm, parallel-group study comparing the efficacy and safety of lixisenatide to sitagliptin as an add-on treatment to metformin in obese patients with T2DM younger than 50 years old.

The primary objective was to assess the efficacy of lixisenatide compared to sitagliptin on a composite endpoint of the percentage of patients with both HbA1c <7% at Week 24 and a weight loss of at least 5% from baseline at Week 24.

A total of 319 patients were randomised (158 in the lixisenatide group and 161 in the sitagliptin group). All patients were treated with at least 1500 mg/day of metformin at baseline.

The percentage of patients with HbA1c<7% at Week 24 and a weight loss of at least 5% of baseline body weight at Week 24 was higher in the lixisenatide group (12.0%) than in the sitagliptin group (7.5%). The treatment difference was not statistically significant (weighted average of response rate difference versus sitagliptin: 4.6%; p=0.1696 based on the primary analysis using the CMH method).

The percentage of patients with HbA1c<7% at Week 24 was 40.7% in the lixisenatide group compared to 40.0% in the sitagliptin group, and percentage of patients with HbA1c≤6.5% was 24.0% in the lixisenatide group compared to 26.3% in the sitagliptin group.

The LS mean changes in HbA1c from baseline to Week 24 in the lixisenatide group was -0.66% and in the sitagliptin group -0.72% (least squares [LS] mean difference versus sitagliptin 0.06%; 95% CI: -0.179%, 0.308%). The percentage of patients who had ≥5% body weight loss from baseline to Week 24 was 18.4% in the lixisenatide group and 11.9% in the sitagliptin group. Patients in the lixisenatide group had a significantly greater decrease in body weight than patients in the sitagliptin group (LS mean difference of -1.34 kg, 95% CI: -2.101 kg to -0.575 kg). The percentages of patients requiring rescue therapy were 9.5% in the lixisenatide group and 6.8% in the sitagliptin group.

Study PDY6797 was a randomized double-blind, placebo-controlled, Phase 2 study assessing the efficacy, safety, and PK of lixisenatide administered for 5 or 6 weeks, either once daily or twice daily, following dose escalation from 5 or 10 to 30 micrograms, as an add-on treatment to SU alone or combined with metformin in Japanese and Caucasian patients with T2DM.

The primary objective was to assess the effect of the highest tolerated dose of lixisenatide administered once daily or twice daily on the increase in $AUC_{[0:29h-4:30h]}$ of postprandial plasma glucose induced by a standardised breakfast. A secondary objective was to assess the treatment-by-ethnicity interaction in Japanese and Caucasian patients on the change in variables assessed after a standardised breakfast (ie, 2-hour PPG, insulin, and glucagon), FPG, HbA_{1c}, and body weight at the highest tolerated doses of lixisenatide. Anti-lixisenatide antibody development was also assessed.

For the $AUC_{[0:29h \text{ to } 4:30h]}$ of PPG, pair-wise adjusted mean differences versus placebo were highly significant in both lixisenatide once and twice daily regimes at the highest well tolerated dose in the per protocol population (-333.4 and -288.8 h.mg/dL, respectively, p<0.0001). The difference was significant in each ethnicity (Japanese patients, -406.7 and -346.3 h.mg/dL; Caucasian patients, -260.1 and -231.3 h.mg/dL, respectively).

The treatment-by-ethnicity interaction test was statistically significant, with a greater decrease seen in Japanese patients (p=0.0074) in the mITT population.

For HbA_{1c} measured on the last day at the highest well-tolerated dose, the LS mean differences versus placebo in changes from baseline were -0.76% for lixisenatide once daily and -0.89% for lixisenatide twice daily in Japanese patients, and -0.31% and -0.56% in Caucasian patients, respectively (per protocol population). The changes in the placebo groups were -0.43% and -0.37% in the Japanese and Caucasian populations, respectively

Study PDY10931 was a randomised, open-label, parallel-group Phase 2 study comparing the effects on PPG of lixisenatide 20 micrograms once daily (1-step dose increase regimen) with liraglutide (starting dose of 0.6 mg daily followed by 1.2 microgram daily for 1 week, then a maintenance dose of 1.8 microgram daily), as an add-on treatment to metformin, in patients with T2DM not adequately controlled with metformin.

The study duration per patient was approximately 4 weeks.

Lixisenatide treatment resulted in a significant mean reduction in postprandial glucose ($GLU\text{-}AUC_{0:30-4:30h}$) from baseline to Day 28 of -227.25 h.mg/dL (95% CI: -246.88 to -207.61), which was larger than the reduction of -72.83 h.mg/dL (95% CI: -93.19 to -52.46) obtained in the liraglutide group. The mean estimate for the difference between the 2 treatments was -154.42 h.mg/dL (95% CI: -180.30 to -128.54) and was statistically significant (p <0.0001).

Mean HbA_{1c} levels decreased in both treatment groups, from 7.20% and 7.41% (baseline) to 6.89% and 6.92% (at Day 28) in the lixisenatide and liraglutide groups, respectively. The estimated treatment difference for the change from baseline was 0.14% (lixisenatide versus liraglutide, p =0.01).

Study EFC10781. During the procedure the applicant has submitted results from a new study (EFC10781) examining the addition of lixisenatide to insulin glargine compared to placebo. At the end of the 24-week treatment period, the mean HbA1c value was reduced in both treatment groups to 6.96% in the lixisenatide group and 7.28% in the placebo group (mean difference -0.32%, CI -0.46% to -0.17%). A significantly higher percentage of patients in the lixisenatide group reached target HbA1c <7 % (56.3% versus 38.5 %, p = 0.0001) or ≤6.5% (32.1% versus 16.3%, p<0.0001) as compared with placebo.

A statistically significant difference in the body weight change from baseline was found between the 2 treatment groups: body weight remained almost unchanged in the lixisenatide group but increased in the placebo group (LS mean body weight change from baseline to Week 24 of 0.28 kg and 1.16 kg, respectively; LS mean difference for lixisenatide versus placebo was -0.89 kg; 95% CI: -1.423, -0.353; p = 0.0012).

Over the 24-week on-treatment period, the daily insulin glargine dose in both groups increased gradually (LS mean change from baseline was 3.10 U in the lixisenatide group and 5.34 U in the placebo group, LS mean difference -2.24 U; 95% CI: -4.264, -0.218; p =0.0300), which was permitted by the protocol to maintain FPGs between 4.4 and 5.6 mmol/L. Concerning safety, TEAEs of hypoglycemia were reported in 27.4% treated with lixisenatide 19.3% on placebo.

Study EFC6017. Another new study (EFC6017) was submitted during the procedure which assessed the efficacy of lixisenatide on glycaemic control in comparison to placebo as add-on treatment to pioglitazone (with or without metformin). For the primary endpoint, change in HbA1c at week 24, the LS mean difference of -0.56% for lixisenatide versus placebo was statistically significant (95% CI: -0.731%, -0.386%; p<0.0001).

The maximal reduction in HbA1c during the whole double-blind treatment period was at Week 36 in both treatment groups and was then largely maintained for the remainder of the study.

2.5.3. Discussion on clinical efficacy

Based on the results of the phase 2 dose finding studies the applicant came to the conclusion that the optimal benefit/risk ratio was observed with the 20 micrograms once daily dose. It is agreed that higher doses did not contribute much with respect to the glucose-lowering effect, but were associated with more adverse events. The results also indicated that lixisenatide was effective whether it was injected once daily in the morning or once daily in the evening.

In the mITT population, the majority of all patients were Caucasian. All patients were Asian in Study EFC10887, as well as 44.7% of patients in Study EFC6015, 22.0% in Study EFC6018, and 16.8% in Study EFC6016. The gender ratio was generally comparable between groups and across placebo-controlled studies, with a range of 48.5% to 56.9% of female patients.

Median age of the study population ranged from 54 to 59 years across pivotal studies. The majority of patients were between 50 and 65 years of age. The percentages of patients ≥65 to <75 years of age ranged from 8.1% to 25.5% and ≥75 years ranged from 0% to 5.2%.

In the monotherapy study (EFC6018) lixisenatide treatment resulted in a placebo adjusted reduction of HbA1c of approx. 0.6% after 12 weeks treatment. This effect size is considered to be of clinical relevance. Concerning the effect on body weight, the mean change was very similar in the placebo and the active group (approx. 2 kg reduction in both groups).

In the placebo controlled add-on to metformin studies (EFC6014 and EFC10743), performed primarily in Caucasian patients, treatment with lixisenatide resulted in statistically significant reductions in HbA1c compared to placebo ranging from 0.37 to 0.49 %. The assessment of the magnitude of the effect in these studies was complicated by a large placebo effect (0.35 and 0.4 %, respectively). In further post hoc analyses of patients recruited in Western and Eastern Europe, the mean placebo corrected effect was a reduction of HbA1c of approximately 0.5 % which is of clinical relevance. Thus, the magnitude of the effect of lixisenatide as add on to metformin was considered of clinical relevance by CHMP. Mean reductions in body weight were smalland the difference compared to placebo was only statistically significant in one of the two studies.

The results in study EFC6017, in which lixisenatide was added to pioglitazone +/- metformin, showed a similar placebo-corrected reduction of HbA1c of -0.56%.

As add on to SU, or SU+metformin, the mean placebo corrected reduction of HbA1c was 0.74 % which is considered a clinically relevant effect, particularly considering that patients already were treated with an insulin secretagogue. Mean reduction in body weight was 1.76 kg in the lixisenatide group. The difference from placebo (-0.93 kg) was statistically significant. This study (EFC6015) included a large

proportion of Asian patients (approx. 45%) in which the placebo corrected glucose-lowering effect was somewhat more pronounced compared to Caucasian patients.

Two studies examined the additive effect of lixisenatide when added to ongoing insulin treatment (with or without metformin and with or without SU). In study EFC6016, the placebo corrected reduction of HbA1c (-0.36%) was statistically significant. Mean body weight was reduced by 1.80 kg in the lixisenatide group. Study EFC 10887 was entirely performed in Asia and the study population differed compared to what is usually seen in Caucasian patients with respect to BMI and insulin doses. In this study, the placebo adjusted reduction in HbA1c was 0.88%, but the effect on body weight was very limited. The benefit (with respect to HbA1c) of adding lixisenatide in comparison to up-titration of the insulin glargine dose in study EFC10781 (submitted during the procedure) was 0.32%. The benefit with respect to body weight was a 0.9 kg lower increase compared to placebo.

The assessment of the magnitude of the effect of lixisenatide added to insulin was hampered by a large placebo effect. However, based on a subgroup analyses of the insulin studies (submitted during the procedure) of patients who could be expected to be adherent to background therapy, a reduction of HbA1c of 0.5-0.6% compared to placebo was considered plausible when lixisenatide is added to insulin. Further, responder rates show an additive effect compared to placebo. Thus, the glucose lowering effect was seen by CHMP to be of relevance also in combination with insulin.

The results of the active controlled study EFC6019, applying the recommended non-inferiority margin of 0.3, indicated that the effect of lixisenatide may be inferior to exenatide. The reduction of HbA1c was larger with exenatide compared to lixisenatide with an upper 95% CI of 0.297% in the predefined mITT and 0.315% in the completer population, respectively. However, the absolute mean reduction of HbA1c with lixisenatide (-0.79%) was of clear clinical relevance. The reduction in body weight was more pronounced for exenatide than for lixisenatide (-3.98 and -2.96 kg, respectively) but of clinical relevance in both groups. The glucose lowering effect of lixisenatide was in general maintained in patients continuing into the extension phases of the studies.

The effect of lixisenatide on plasma glucose parameters was statistically significantly larger compared to placebo in all studies. In one phase 2 study, lixisenatide was more effective in lowering post prandial glucose compared to liraglutide after 28 days of treatment.

The results of some of the phase 3 studies indicate a difference in effect between Asian and Caucasian patients. This was further examined in the phase 2 study PDY6797. Also in this study, the effect of lixisenatide was more pronounced in Japanese patients compared to Caucasians and the treatment-by-ethnicity interaction test was statistically significant, with a greater decrease in post prandial glucose seen in Japanese patients. This may be explained by the fact that Japanese patients had a lower BMI and higher insulin sensitivity at baseline. Japanese patients also had higher concentrations of lixisenatide which in turn was likely due to the lower mean body weight of the Japanese patients. However, the glucose lowering effect is considered to be of relevance also in Caucasian patients.

Pooled analyses of anti-lixisenatide antibody status showed that at the end of the main treatment period (Week 24), 69.4% of evaluable patients were assessed as antibody-positive. For those with the highest antibody concentrations, the mean HbA1c reducing effect was attenuated. However, as no correlation between antibody concentration categories and change in HbA_{1c} was seen (i.e. patients with high antibody concentrations can have adequate as well as attenuated response to lixisenatide) , antibody status cannot be used for prediction of the glucose lowering effect of lixisenatide. These findings are very similar to those previously seen with exenatide.

Apart from the difference in effect in Asian and Caucasian patients, no striking differences between subgroups have been identified. The number of patients above 75 years of age was limited (n=56). The number of patients with moderate and severe renal impairment was also very limited.

2.5.4. Conclusions on the clinical efficacy

Treatment with lixisenatide as monotherapy or add on to other glucose-lowering therapies, resulted in absolute reductions in HbA1c ranging from -0.74 to -0.92% (12-24 weeks of treatment). The placebo adjusted reductions ranged from -0.36 to -0.88%. This magnitude of glucose lowering effect is considered as clinically relevant.

Concerning non-inferiority compared to exenatide, this has not been robustly shown with respect to reduction of HbA1c and weight reduction. However, the absolute mean reduction of HbA1c with lixisenatide (-0.79%) as well as weight reduction (-2.8 kg) in the comparative study is of clear clinical relevance. Further, lack of proof of non inferiority could be acceptable considering other benefits such as once daily dosing and a lower incidence of hypoglycaemia and nausea (as described in the Safety Section of this report) in the comparative study.

Overall, the mean difference in body weight with lixisenatide compared to placebo was approximately 1 kg. In the diabetic population, reduction of body weight is always of clinical relevance and advantageous compared to the increase in weight with some other therapeutic options.
In conclusion, the effects of lixisenatide on glucose parameters and body weight are considered to be of clear clinical relevance.

2.6. Clinical safety

The primary safety data base, cut-off date of 30 April 2011, consists of safety data from 26 of the completed studies, 13 Phase 2/3 studies and 13 clinical pharmacology studies. The data from the Phase 2 and 3 studies are pooled into 2 main groups, and the studies included in these pools are listed below. At the secondary data cut-off date of 01 July 2011 for reporting deaths and serious adverse events (SAE), 2460 patients/subjects were randomised in ongoing studies: 484 in Study EFC6017, 446 in Study EFC10781, 376 in Study EFC11321, 595 in Study EFC11319, 275 in Study TDR11215, 264 in Study TES11807 and 20 in Study PDY11824.

Trials not included in the integrated database included 8 completed clinical pharmacology studies (3 studies in special populations, 1 prolonged release formulation study, 4 combination studies with lixisenatide and insulin glargine), 4 ongoing Phase 3 studies (including the CV outcome study) and 3 ongoing clinical pharmacology studies. Regarding the Phase 3 studies, the data analyses were ongoing for study EFC6017 at the time of the MAA submission and for studies EFC10781, EFC11321, and EFC11319 it was stated to remain blinded. The data from these studies have been discussed separately, where applicable.

The comparative assessment of the clinical safety of lixisenatide is primarily based on the Phase 2/3 studies pool and the Phase 3 placebo controlled studies pool.

Patient exposure

At least 1 dose of lixisenatide was given to the 3304 patients included in the primary safety population, i.e. patients in the pool Phase 2/3 studies. A majority (78%) of the lixisenatide-treated patients was exposed to a mean daily dose of >17.5 micrograms, i.e. to the recommended dosage regimen of lixisenatide. Of the 3304 patients, 2059 patients (78%) were exposed for at least 6 months (≥169 days), 1692 (51%) for at least 1 year (≥365 days), 1233 (37%) for at least 18 months (≥547 days), and 197 (6.0%) for at least 2 years (≥729 days). See Table below.

Total lixisenatide exposure for the lixisenatide treated subject in the Phase 2/3 studies was 3286 subject-years with a mean exposure per subject of 1.0 years. Total lixisenatide exposure for the

lixisenatide treated subjects in the placebo controlled phase 3 studies was 2587 subject-years with a mean exposure per subject of 1.2 years.

Table 15 - Patient exposure (cut off date of 30 April 2011) - Safety population

	Patients enrolled	Patients exposed	Patients exposed to mean dose of >17.5µg	Patients with long term safety data > 52 weeks/>78 weeks />104 weeks
Placebo-controlled (Phase 3)[a]	3188	2127	1791[e]	1387/1057/185
Active-controlled (Phase 3)[b]	953	476	419	248/176/12
Open (Phase 3)[c]	69	69	50	57/-/-
Placebo/active control/open (Phase 2)[d]	874	632	312	
Grand total Phase 2/3 population		***3304***	***2590***[f]	***1692/1233/197***
Clinical pharmacology	462	404	347	
Grand total primary safety data base		*3708*	*2937*	

[a] EFC6014, EFC6015, EFC6016, EFC6018, EFC10743, EFC10887; [b] EFC10780, EFC6019 (Open); [c] LTS10888; [d] ACT6011, PDY6797, DR16012, PDY10931 [e] Cumulative exposure: 2586.8 patient-years; mean exposure 444.2 (SD 251.0) days /subject [f] Cumulative exposure: 3286.1 patient-years; mean exposure 363.3 (SD 264.5) days /subject

Adverse events

The summary of adverse events reported by at least 5% of lixisenatide-treated subjects in the Phase 2/3 study populations is shown in the Table below.

Table 16 - Adverse events reported by at least 5% of lixisenatide-treated subjects (Safety population Phase 2/3 studies)

	Controlled					Controlled + uncontrolled
	Placebo-controlled[a]		All controlled[b]		Uncontrolled[c]	
System Organ Class Preferred Term n(%)	Placebo (N=1232)	Lixisenatide (N=2682)	Lixisenatide (N=3235)	All comparators (N=1780)	Lixisenatide (N=69)	Lixisenatide (N=3304)
Any event	895 (72.6%)	2101 (78.3%)	2504 (77.4%)	1309 (73.5%)	63 (91.3%)	2567 (77.7%)
Infections and infestations	445 (36.1%)	918 (34.2%)	1110 (34.3%)	631 (35.4%)	29 (42.0%)	1139 (34.5%)
Nasopharyngitis	160 (13.0%)	259 (9.7%)	321 (9.9%)	212 (11.9%)	22 (31.9%)	343 (10.4%)
Influenza	61 (5.0%)	160 (6.0%)	197 (6.1%)	98 (5.5%)	1 (1.4%)	198 (6.0%)
Upper respiratory tract infection	57 (4.6%)	134 (5.0%)	155 (4.8%)	76 (4.3%)	0	155 (4.7%)
Metabolism and nutrition disorders	257 (20.9%)	643 (24.0%)	717 (22.2%)	363 (20.4%)	15 (21.7%)	732 (22.2%)
Hypoglycaemia	184 (14.9%)	458 (17.1%)	478 (14.8%)	237 (13.3%)	6 (8.7%)	484 (14.6%)
Psychiatric disorders	63 (5.1%)	182 (6.8%)	238 (7.4%)	90 (5.1%)	0	238 (7.2%)
Nervous system disorders	271 (22.0%)	702 (26.2%)	819 (25.3%)	377 (21.2%)	12 (17.4%)	831 (25.2%)
Headache	125 (10.1%)	320 (11.9%)	395 (12.2%)	182 (10.2%)	2 (2.9%)	397 (12.0%)
Dizziness	81 (6.6%)	216 (8.1%)	246 (7.6%)	121 (6.8%)	2 (2.9%)	248 (7.5%)
Eye disorders	69 (5.6%)	158 (5.9%)	184 (5.7%)	87 (4.9%)	7 (10.1%)	191 (5.8%)
Cardiac disorders	53 (4.3%)	154 (5.7%)	173 (5.3%)	70 (3.9%)	1 (1.4%)	174 (5.3%)

Vascular disorders	83 (6.7%)	186 (6.9%)	214 (6.6%)	108 (6.1%)	1 (1.4%)	215 (6.5%)
Respiratory, thoracic and mediastinal disorders	103 (8.4%)	220 (8.2%)	262 (8.1%)	142 (8.0%)	4 (5.8%)	266 (8.1%)
Gastrointestinal disorders	304 (24.7%)	1244 (46.4%)	1483 (45.8%)	548 (30.8%)	51 (73.9%)	1534 (46.4%)
Nausea	90 (7.3%)	721 (26.9%)	857 (26.5%)	236 (13.3%)	30 (43.5%)	887 (26.8%)
Vomiting	33 (2.7%)	307 (11.4%)	363 (11.2%)	87 (4.9%)	5 (7.2%)	368 (11.1%)
Diarrhoea	98 (8.0%)	299 (11.1%)	363 (11.2%)	175 (9.8%)	4 (5.8%)	367 (11.1%)
Dyspepsia	11 (0.9%)	133 (5.0%)	161 (5.0%)	47 (2.6%)	5 (7.2%)	166 (5.0%)
Constipation	30 (2.4%)	104 (3.9%)	122 (3.8%)	53 (3.0%)	5 (7.2%)	127 (3.8%)
Abdominal pain upper	23 (1.9%)	89 (3.3%)	111 (3.4%)	44 (2.5%)	4 (5.8%)	115 (3.5%)
Abdominal discomfort	14 (1.1%)	41 (1.5%)	45 (1.4%)	20 (1.1%)	11 (15.9%)	56 (1.7%)
Skin and subcutaneous tissue disorders	109 (8.8%)	242 (9.0%)	289 (8.9%)	144 (8.1%)	11 (15.9%)	300 (9.1%)
Musculoskeletal and connective tissue disorders	211 (17.1%)	539 (20.1%)	630 (19.5%)	291 (16.3%)	8 (11.6%)	638 (19.3%)
Back pain	55 (4.5%)	161 (6.0%)	188 (5.8%)	83 (4.7%)	3 (4.3%)	191 (5.8%)
General disorders and administration site conditions	151 (12.3%)	498 (18.6%)	591 (18.3%)	225 (12.6%)	17 (24.6%)	608 (18.4%)
Fatigue	29 (2.4%)	87 (3.2%)	111 (3.4%)	44 (2.5%)	4 (5.8%)	115 (3.5%)
Investigations	105 (8.5%)	225 (8.4%)	274 (8.5%)	159 (8.9%)	4 (5.8%)	278 (8.4%)
Injury, poisoning and procedural complications	120 (9.7%)	249 (9.3%)	291 (9.0%)	156 (8.8%)	11 (15.9%)	302 (9.1%)
Contusion	16 (1.3%)	39 (1.5%)	46 (1.4%)	16 (0.9%)	5 (7.2%)	51 (1.5%)

[a] Studies included: ACT6011, PDY6797, DRI6012, EFC6014, EFC6015, EFC6016, EFC6018, EFC10743 and EFC10887. [b] Studies included placebo-controlled studies plus active-controlled studies (PDY10931, EFC6019 and EFC10780). [c] LTS10888.
All lixisenatide dose groups were included. All comparators: placebo, exenatide, liraglutide and sitagliptin. TEAE: Treatment emergent adverse event.
PGM=PRODOPS/AVE0010/OVERALL/CTD_2011_01/REPORT/PGM/ae_soc_t.sas OUT=REPORT/OUTPUT/ae_soc_t_pt_p23all_x.rtf (19AUG2011 - 9:41)

The most common adverse events associated with lixisenatide are nausea (26%), vomiting (10.5%) and diarrhoea (8.3%). This is not unexpected since gastrointestinal adverse events are common among GLP-1 receptor agonists.

In addition, the adverse events occurring with a frequency ≥2% for the lixisenatide group and >1.5 times the incidence in placebo in the Phase 3 placebo controlled group were injection site reactions, decreased appetite, tremor, dyspepsia, and abdominal distension.

Serious adverse event/deaths/other significant events

In the pool of all Phase 2/3 studies, a total of 233 (7.9%) lixisenatide-treated patients reported SAEs compared with 128 (7.3%) patients in the all-comparators group (includes 103 placebo patients). The reporting of SAEs was comparable between the treatment groups.

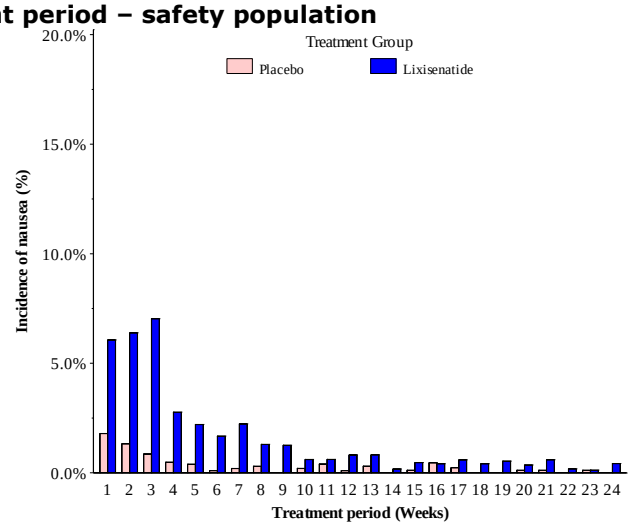
In the pool of all Phase 2/3 studies, a total of 16 (0.5%) deaths were reported in the lixisenatide group compared with 11 (0.6%) deaths in the all-comparator groups. Of these, 5 deaths in the lixisenatide group and 3 in the all-comparators group occurred due to a post treatment AE. The overall mortality rate per 100 patient years was similar between the lixisenatide group (0.5) and the all comparator group (0.6).

Significant adverse events

Nausea and vomiting

The most common adverse events associated with lixisenatide are nausea (26%) and vomiting (10.5%) which mostly were mild to moderate in intensity. The onset and peak were within the first 3 weeks and thereafter the incidence decreased. Approximately 70-80% of the patients experiencing nausea or vomiting completed the treatment. In the active controlled study versus exenatide (EFC6019), the incidence rate of nausea was 24.5% in the lixisenatide group compared to 35.1% for exenatide.

Figure 3 - Incidence (%) of patients with nausea by week in Phase 3 placebo controlled studies: main treatment period – safety population



Studies included: EFC6014, EFC6015, EFC6016, EFC6018, EFC10743, and EFC10887

In study DRI6012, a clear dose-response relationship was seen in the number of subjects with nausea: frequencies were 7.3% (5 micrograms), 11.5% (10 micrograms), 25.5% (20 micrograms) and 35.2% (30 micrograms) in lixisenatide once-daily groups. The onset of the gastrointestinal TEAE episodes (nausea, vomiting, diarrhea) decreased with time (appeared mostly during the first 3 to 6 weeks of the treatment), and were usually mild to moderate in intensity. To reduce the incidence of GI adverse events, a lower starting dose is recommended.

Hypoglycaemia

The incidence of symptomatic hypoglycaemia was 1.7% when lixisenatide was used as monotherapy (placebo 1.6%). In combination with metformin, symptomatic hypoglycaemia occurred in 7.0% of lixisenatide patients and in 4.8% of placebo patients.
In patients taking lixisenatide in combination with an SU and metformin, symptomatic hypoglycaemia occurred in 22.0% of lixisenatide treated patients and in 18.4% of placebo treated patients. In combination with a basal insulin with or without metformin, symptomatic hypoglycaemia occurred in 42.1% of lixisenatide patients and in 38.9% of placebo patients.
When lixisenatide was given with a sulphonylurea alone, symptomatic hypoglycaemia occurred in 22.7% of lixisenatide treated patients versus 15.2% with placebo. Given with a sulphonylurea and a basal insulin, symptomatic hypoglycaemia occurred in 47.2% of lixisenatide treated patients compared to 21.6% with placebo.
Overall, the incidence of severe symptomatic hypoglycaemia was uncommon (0.4% in lixisenatide patients and 0.2% in placebo patients) during the entire treatment period of the phase 3 placebo-controlled studies.

The incidence of symptomatic hypoglycaemia was 2.5 %for lixisenatide compared to 7.9% for exenatide in the comparative study.

Cardiovascular events

The incidence of cardiac disorders adverse events was 6.2% in the lixisenatide group compared to 4.4% in the placebo group. The incidences of specific events compared to placebo were: palpitations 1.5% vs 0.6%, tachycardia 0.7% vs <0.1%, supraventricular arrhythmias 1.1% versus 0.7%, cardiac conduction disorders 0.6% versus 0.1%.

Concerning effect on QT, see the Section Clinical Pharmacology in this report.

In the QT/QTc study TES11807, an increased heart rate (+7.3 bpm) was associated with the use of lixisenatide at maintenance therapeutic doses in healthy volunteers. The increase in heart rate started approximately 1 hour after dosing and continued to approximately 10 hours after dosing. In the phase 3 studies no mean increase in heart rate was reported. Heart rate is monitored in the ongoing CV outcome study. Information regarding the increased heart in healthy volunteers has been included in SmPC section 4.8.

A meta analysis of CV events has been submitted during the procedure, including the results of the studies EFC6017 and EFC10781. The results of the meta analysis of major cardiovascular events (MACE) (CV death, non fatal myocardial infarction and stroke, positively adjudicated by the Cardiovascular Events Adjudication Committee [CAC]) versus placebo was HR 1.25 (95% confidence interval 0.67-2.35). The increase in MACE was driven by a difference in non fatal stroke (0.7% versus 0.4% for placebo). The incidence of other MACE endpoints did not differ between lixisenatide and placebo.

Further data on CV safety will be captured in the ongoing long term (176 weeks) cardiovascular outcome study (study EFC11319; ELIXA) in type 2 diabetic patients who experienced an acute coronary syndrome event within 180 days prior to screening. The study was initiated in June 2010 and the planned number of patients is 6000 (). The study is ongoing with an expected date of completion in Q4 2014.

Neoplasms

In the non-clinical program with lixisenatide, proliferative thyroid C-cell effects at very high exposure ratios (C-cell hyperplasia at exposure ratios ≥272 and C-cell adenoma at exposure ratios ≥913, both in rats and mice, and C-cell carcinoma at exposure ratios ≥4370 exclusively in rats but not in mice) were observed in 2-year carcinogenicity studies with lixisenatide in mice and rats. This has also been seen for other products within the GLP-1 receptor agonist class.

In the pool of all Phase 2/3 studies, thyroid neoplasms (including PT benign neoplasm of thyroid gland) were reported in 13 (0.4%) patients given lixisenatide and 4 (0.3%) in the placebo group. No thyroid cancer was reported in lixisenatide-treated group. Monitoring of serum calcitonin as a marker of thyroid C-cell neoplasms was implemented in all lixisenatide studies more than 3 months in duration or completed prior to 2009. There were no indications of altered calcitonin levels over time in the studies. Pancreatic carcinoma was reported by 3 (<0.1%) lixisenatide patients and 1 (<0.1%) patient in the comparator group. Thus, no trends could be observed. However, the risk for developing malignancies cannot be fully explored from data from short term studies. Malignancies will be monitored in ongoing studies as well as in planned epidemiological studies.

Pancreatitis

Pancreatitis has been previously identified as a potential safety issues for the GLP-1 receptor agonist class. Overall there were more patients in the lixisenatide group [9 (0.3%)], when compared to the all

comparators group [2 (0.1%)], who experienced AEs specific to pancreatitis (Class 2) such as pancreatitis, pancreatitis acute and pancreatitis chronic. In some instances the reported investigator verbatim term was "suspected pancreatitis", which was coded to the PT of pancreatitis due to limitations of the MedDRA dictionary. When the events of pancreatitis acute and pancreatitis were confirmed, by either gastroenterologic consultation or positive imaging studies, the incidence was similar between the treatment groups. However, the duration of treatment is too short to properly address the issue. The risk of pancreatitis in patients treated with GLP-1 analogues may be low but it may be related to the mechanism of action. Acute pancreatitis is included as an important potential risk in the RMP which was endorsed by CHMP and is mentioned in section 4.4 of the SmPC.

Acute renal failure

There were 4 patients who reported serious TEAEs of renal failure in the Phase 2/3 studies (1 in the lixisenatide, 2 in the placebo group and 1 in the sitagliptin group). The lixisenatide- treated patient experienced acute renal failure secondary to cocaine abuse.

Injection site reactions

In all controlled studies in the Phase 2/3 pool, the incidence of injection site reaction was 5.3% in the lixisenatide group and 1.9% in the all-comparator group (placebo + active). The most frequently reported injection site reactions (>1% incidence) with lixisenatide versus all comparators were injection site pruritus (1.2% versus 0%) and injection site pain (1.1% versus 0.6%). No severe or serious TEAEs related to injection site reactions were reported. Nine out of 2950 patients discontinued lixisenatide treatment due to an injection site reaction. In the main treatment period of the Phase 3 placebo-controlled studies, the incidence of injection site reaction was 3.9% in the lixisenatide group and 1.4% in the placebo group. In the comparative study with exenatide, the incidence of injection site reactions was 9.1 and 2.2% for lixisenatide and exenatide, respectively.

Laboratory findings

No clinically meaningful changes from baseline to last visit were noted in haematology parameters, chemistry or urinary analysis. No relevant mean changes were observed for liver tests, renal function, or serum lipid values over time compared to baseline values in both treatment groups during the entire treatment period in the Phase 3 placebo-controlled studies. Significant increases in liver tests, renal parameters, or lipid values occurred in a limited number of patients, with a similar incidence between lixisenatide group and placebo group for all parameters.

Safety in special populations

Age

In general, there seem to be no differences in safety between the age groups. Few patients (lixisenatide N=48, placebo N=31) in age group ≥75 years were enrolled in the studies and this has been reflected in SmPC section 4.2. In the age group ≥ 65 to < 75 a total of 331 patients were treated with lixisenatide.

Table 17 - Related TEAEs by age group in Phase 3 placebo-controlled studies: Entire treatment period Safety population

	Age <65		Age 65-74		Age 75-84		Age >=85	
	Placebo (N=817)	Lixisenatide (N=1748)	Placebo (N=213)	Lixisenatide (N=331)	Placebo (N=30)	Lixisenatide (N=47)	Placebo (N=1)	Lixisenatide (N=1)
Patients with any related TEAE	214 (26.2%)	766 (43.8%)	63 (29.6%)	166 (50.2%)	8 (26.7%)	27 (57.4%)	0	1 (100%)
Patients with any related serious TEAE	6 (0.7%)	13 (0.7%)	5 (2.3%)	2 (0.6%)	0	3 (6.4%)	0	0
SAE by outcome	6 (0.7%)	13 (0.7%)	5 (2.3%)	2 (0.6%)	0	3 (6.4%)	0	0
Results in Death	0	0	1 (0.5%)	0	0	0	0	0
Requires or prolong hospitalization	3 (0.4%)	9 (0.5%)	4 (1.9%)	1 (0.3%)	0	1 (2.1%)	0	0
Congenital anomaly or Birth defect	0	0	0	0	0	0	0	0
Life threatening	1 (0.1%)	0	0	0	0	0	0	0
Persist./signify. Disability/incapacity	0	0	0	0	0	0	0	0
Other medically important event	4 (0.5%)	4 (0.2%)	0	1 (0.3%)	0	2 (4.3%)	0	0
Drug withdrawal (SMQ)	0	0	0	0	0	0	0	0
Psychiatric disorders (SOC)	3 (0.4%)	22 (1.3%)	0	3 (0.9%)	0	0	0	0
Nervous system disorders (SOC)	39 (4.8%)	157 (9.0%)	9 (4.2%)	35 (10.6%)	1 (3.3%)	9 (19.1%)	0	0
Accidents and injuries (SMQ)	4 (0.5%)	1 (<0.1%)	1 (0.5%)	1 (0.3%)	0	0	0	0
Cardiac disorders (SOC)	4 (0.5%)	13 (0.7%)	4 (1.9%)	3 (0.9%)	0	0	0	0
Vascular disorders (SOC)	3 (0.4%)	11 (0.6%)	3 (1.4%)	2 (0.6%)	0	1 (2.1%)	0	0
Cerebrovascular disorders (SMQ)	0	0	0	0	0	1 (2.1%)	0	0
Infections and infestations (SOC)	5 (0.6%)	15 (0.9%)	1 (0.5%)	0	1 (3.3%)	0	0	0
Quality of life decreased (PT)	0	0	0	0	0	0	0	0

TEAE=treatment Emergent Adverse Event
Studies included: EFC6014, EFC6015, EFC6016, EFC6018, EFC10743 and EFC10887
PGM=DEVOPS/AVE0010/OVERALL/EMEA_2012_MAR/REPORT/PGM/ae_rsoc_smq_age_24w_t.sas OUT=REPORT/OUTPUT/ae_rsoc_smq_age_24w_t_i.rtf (05APR2012 - 11:25)

Gender

The frequency of nausea- and vomiting-related events was higher in female patients compared to males in both lixisenatide and placebo groups.

Race

Higher incidences of nausea, vomiting and hypoglycaemia are seen in treated Asian/Oriental patients (with add on to basal insulin or insulin+SU as a background therapy) in comparison with Caucasian patients. With regard to Black patients, a total of 230 Black patients have been included in Phase 2-3 controlled studies completed so far (142 exposed to lixisenatide and 88 in the all comparators group).

Renal function

A very low number of patients with moderate renal impairment (N=28/lixisenatide) were included in phase 3 studies. TEAEs were higher in patients with mild renal impairment than in patients with normal renal function, and there is a trend for an increased incidence of TEAEs in patients with moderate renal impairment. Additional analyses were performed on a subgroup of patients with either moderate or severe renal impairment and with body mass index (BMI) <25 kg/m^2. In this specific population with moderate renal impairment, some adverse events (specifically nausea and headache) were more frequently reported than in the general population, although, hypoglycaemia was less frequently reported in the lixisenatide group than in the placebo group. Only few events were serious or led to discontinuation. The data is scarce and it is difficult to draw any firm conclusions from the reported safety data. Given the signal of a slight increase in adverse events in mild renal impairment and very limited clinical experience in moderate renal impairment it is reasonable to recommend use with caution in patients with moderate renal impairment.

Antibody data

In lixisenatide-treated patients the proportion of patients with positive antibody 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. At Week 24, antibody concentration was measured in 710 of 719 antibody-positive patients and was found to be <LLOQ in 503 (70.8%) of them. At Week 76, 45.0% of antibody-positive patients had an antibody concentration >LLOQ. The majority of the patients (67%) who discontinued were still positive after 3-6 months.

In Study EFC6015, no cross-reactivity of the antibodies with endogenous GLP-1or glucagon, was seen in any of the patients.

The effect of anti-lixisenatide antibody data on safety

In the lixisenatide-treated group there was a higher incidence of TEAEs in the antibody-positive group (83.2%) compared to the antibody-negative group (74.7%) during the entire treatment period in the Phase 3 placebo-controlled studies. However, there was no imbalance with respect to antibody status in the incidence of common TEAEs including gastrointestinal disorders, dizziness, headache and upper respiratory tract infection. The incidence of injection site reaction by anti-lixisenatide antibody status was reported as 4.7% in antibody-positive and 2.5% in antibody-negative patients during the entire treatment period. Injection site pruritus, 1.9% (vs 0.4% placebo), injection site erythema 1.1% (vs 0% in placebo) were most prominent.

Allergic reactions

In the pool of all Phase 2/3 studies including studies EFC6017 and EFC10781, 56 (1.8%) lixisenatide patients and 19 (1.2%) placebo patients had events adjudicated by the ARAC as allergic reactions over the entire treatment period.

Allergic reactions adjudicated as possibly related to the investigational product were reported in 0.4% of lixisenatide patients compared with less than 0.1% of placebo patients during the main 24-week treatment period.

A total of 8 cases (0.2%) of anaphylactic reactions were adjudicated as possibly related to treatment in the lixisenatide group in controlled phase II/III studies versus none in the comparator group. In addition, 1 event of anaphylactoid reaction was reported in study EFC11321 which has recently been finalised. With the exception of the case reported in study EFC11321, the hypersensitivity reactions that were adjudicated by ARAC as anaphylactic reactions related to lixisenatide were mostly low grade in severity. None of the events required overnight hospitalization or airway protection. All of the 8 events resolved rapidly, with limited specific corrective treatment, and all patients recovered without sequelae. A positive allergic history was reported for 3 of the patients. Three events were reported in patients with negative antibody status or concentration < LLOQ, 1 in a patient with a positive antibody status but no evaluation of antibody concentration, and 3 events were reported in patients with antibody concentration > 15.50 nmol/L. Urticaria was observed in 10 patients in the lixisenatide group (0.3%) vs 2 in the all-comparator group (<0.1%) and angioedema was seen in 4 patients in the lixisenatide group (0.1%) vs 2 in the all-comparator group (<0.1%).

Safety related to drug-drug interactions and other interactions

The most commonly used nondiabetic concomitant drugs were angiotensin-converting enzyme inhibitors, antithrombotic agents, and statins and statin combinations. No apparent trends in adverse events were in general observed.

Discontinuation due to adverse events

In all controlled studies in the Phase 2/3 pool, the rate of treatment discontinuation in the lixisenatide group was 9.1% compared with 6.3% in the all-comparators group (placebo + active). Overall, the treatment discontinuation rate in the lixisenatide group was similar to that reported in Phase 3 placebo-controlled studies. The main AEs which led to treatment discontinuation in the lixisenatide group (and that occurred at a higher rate compared to placebo) were nausea (3.1%), vomiting (1.2%), dizziness (0.5%), diarrhea (0.4%), hypoglycaemia (0.4%), decreased appetite (0.2%), fatigue (0.2%), and asthenia (0.2%).

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Overall, 2590 patients have been exposed to lixisenatide 20 micrograms once daily out of which 1233 have been exposed to lixisenatide once daily for at least 76 weeks. A total of 197 patients were exposed for at least 104 weeks. The majority of the patients (55%, N=1827) were exposed to the combination of lixisenatide and metformin. The percentage of patients with no background therapy, SU+metformin and basal insulin+metformin was 9.3% (N=308), 16.8% (N=556), 7.9% (N=261), respectively. The other background medications were approximately 3-4% (N=100-130). Thus, an adequate number of patients are exposed for at least 76-104 weeks and the database is in general considered sufficient.

As for other GLP-1 agonists, the most common adverse events reported for lixisenatide are gastrointestinal side effects ; e.g. nausea (26%), vomiting (10.5%) and diarrhoea (8.3%). The product information includes a recommendation concerning a gradual up-titration of the dose to reduce these symptoms. Gastrointestinal events (i.e. nausea, vomiting) are included in the RMP as important identified risks. The incidence is gradually reduced with treatment duration.

Injection site reactions, decreased appetite, tremor, dyspepsia, and abdominal distension were associated with lixisenatide treatment and were also present with a frequency ≥2% for the lixisenatide group and >1.5 times the incidence in placebo in the Phase 3 placebo controlled studies.

In lixisenatide-treated patients the proportion of subjects that developed anti-lixisenatide antibodies 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. The majority of the patients (67%) who discontinued were still positive after 3-6 months. The antibody development will be further assessed in studies post-approval.

Patients positive for anti-lixisenatide antibodies were at higher risk for developing injection site reactions compared with those without antibodies. This has also been reported for exenatide. There were no differences for other adverse events.

Allergic reactions possibly associated with lixisenatide were reported in 0.4% of lixisenatide patients compared with less than 0.1% of placebo patients during the main 24-week treatment period in phase 3 studies. Anaphylactic reactions were observed in 8 patients in the lixisenatide group (0.2%) vs none in the all-comparator group (0%). A positive allergic history was reported for 3 of the patients. Three events were reported in patients with negative antibody status or concentration < LLOQ, 1 in a patient with a positive antibody status but no evaluation of antibody concentration, and 3 events were reported in patients with antibody concentration> 15.50 nmol/L. Thus, the relation between antibody status and allergic reactions is not obvious.

Systemic hypersensitivity reactions are included in the RMP as an important identified risk.

Hypoglycaemia is mainly seen when lixisenatide treatment is combined with SU and/or insulin. The product information states that when lixisenatide is added to SU therapy or insulin a reduction of dose of the SU or the basal insulin may be considered to reduce the risk of hypoglycaemia. Also based on the finding of increased hypoglycaemic rate when using Lyxumia in combination with SU and insulin, the use of lixisenatide in combination with SU and insulin is not recommended. This is reflected in the SmPC section 4.4. . Hypoglycaemia [when used with a sulfonylurea (SU) or with a basal insulin] is included in the RMP as an important identified risk.

Potential long term risks

There is no preclinical or mechanistic rationale to suspect that lixisenatide would increase the risk of cardiovascular events. The QT studies do not indicate a QT-prolonging effect.

There was a higher reported incidence of cardiovascular adverse events in the lixisenatide group (6.2%) when compared to the placebo group (4.2%), mainly palpitations and tachycardia. In the QT/QTc study TES11807, a transient increase in heart rate (+7.3 bpm) was noted in healthy volunteers. However, in the phase 3 studies, no mean increase in heart rate was noted. A propensity for heart-rate increase has been reported for other GLP-1 receptor agonists and based on available data there is no evidence that the effect is more pronounced for lixisenatide. Information regarding the increased heart rate is included in SmPC section 4.8. In addition, more information with regard to CV effects will be obtained in the ongoing CV outcome study EFC11319 which is an additional pharmacovigilance activity of the RMP.

A meta-analysis of CV events has been performed by the applicant on the composite CV endpoints in phase 3 controlled studies (including the results of studies EFC6017 and EFC10781), using a Cox model stratified by study. For major cardiovascular events (MACE; CV death, non-fatal myocardial infarction, and stroke) positively adjudicated by CAC, this showed a HR of 1.25 (95% confidence interval 0.67-2.35) versus placebo. However, the increase in MACE with the use of lixisenatide was driven by a difference in non fatal stroke (0.7% versus 0.4% for placebo). The incidence of other MACE endpoints did not differ between lixisenatide and placebo. The long term (176 weeks) cardiovascular outcome study (EFC11319; study ELIXA) will evaluate CV outcomes with 20 micrograms QD compared to placebo (composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina) in type 2 diabetic patients who experienced an acute coronary syndrome event within 180 days prior to the screening visit. The study was initiated in June 2010 and the planned number of patients is 6000. This ongoing study is an additional pharmacovigilance activity of the RMP with an expected date of completion in Q4 2014.

GLP-1 receptor agonists, including lixisenatide, are associated with thyroid C-cell proliferative/hyperplasia effects in non-clinical carcinogenicity studies. In the clinical development program there was no indication of trends in the incidences of thyroid neoplasms (benign and malignant) in the lixisenatide group in comparison to placebo or the all comparator-group. Monitoring of serum calcitonin as a marker of thyroid C-cell neoplasms was implemented in all lixisenatide studies longer than 3 months in duration or studies completed prior to 2009. Mean and median calcitonin levels remained stable over time and other laboratory assessments did not reveal a clinical safety signal for treatment with lixisenatide regarding thyroid tumors. Pancreatic carcinoma was reported by 3 (<0.1%) lixisenatide patients and 1 (<0.1%) patient in the comparator group. Thus, no trends could be observed. Medullary thyroid cancer and malignant neoplasm are included as important potential risks in the RMP and will be followed in ongoing studies and epidemiological studies. Also the SmPC section 5.3 includes information on the proliferative effects shown in the non-clinical studies.

Acute pancreatitis has been previously identified as a potential safety issue for the GLP-1 receptor agonist class based on cases of acute pancreatitis reported with the use of marketed GLP-1 receptor agonists. The incidence was low in the clinical studies. However, the duration of treatment is too short to properly address the issue. Appropriate information is included in product information. The risk for acute pancreatitis is included as an important potential risk in the RMP section and will be further investigated post-approval

The clinical experience in patients > 75 years is very limited which is reflected in the SmPC.

A very low number of patients with moderate renal impairment (N=28/lixisenatide) were included in phase 3 studies. The data is scarce and it is difficult to draw any firm conclusions from the reported safety data. Given the signal of a slight increase in adverse events in mild renal impairment and very limited clinical experience in moderate renal impairment it is reasonable to recommend use with caution in patients with moderate renal impairment. There is no experience in patients with severe renal impairment. This is reflected in the SmPC.

2.6.2. Conclusions on the clinical safety

Short term safety issues associated with lixisenatide mainly comprise gastrointestinal adverse events which are a known class effect for GLP-1 analogues. Hypoglycaemia is reported mainly in combination with SU and/or insulin. There was no mean increase in heart rate in the clinical studies but a tendency to transient increase in heart rate in the QT study. This has also been reported for other products in the class. More information with regard to CV effects will be obtained in the ongoing CV outcome study. The proportion of patients developing antibodies was 70% for lixisenatide. The development of antibodies has been associated with a higher incidence of injection site reactions (also seen for other products in the class). However, the incidence of allergic reactions possibly associated with lixisenatide was low (0.4%) and the anaphylactic reactions reported were mostly low-grade in severity. Hypersensitivity reactions will be reviewed and continually adjudicated in ongoing trials.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Gastrointestinal events i.e. nausea, vomiting	Routine pharmacovigilance	**Labeling** **SPC Section** *4.8 Undesirable effects* "The most frequently reported adverse reactions during clinical studies were nausea, vomiting, and diarrhoea. These reactions were mostly mild and transient." "Nausea," "vomiting," and "diarrhoea" are listed in ADR table as very common *Gastrointestinal disorders* "Nausea and vomiting were the most frequently reported adverse reactions during the main 24-week treatment period. The incidence of nausea was higher in the lixisenatide group (26.1 %) compared to the placebo group (6.2 %) and the incidence of vomiting was higher in the lixisenatide group (10.5 %) than in the placebo group (1.8 %). They were mostly mild and transient and occured during the first 3 weeks after starting treatment. Thereafter, they progressively decreased during the following weeks." *Withdrawal* "The most common adverse reactions which led to treatment discontinuation in the lixisenatide group were nausea (3.1%) and vomiting (1.2%)."
Systemic hypersensitivity reactions	Routine pharmacovigilance Special attention in PSURs Further evaluation in ongoing and planned clinical trials (EFC11319/ELIXA, EFC12382, EFC12261, EFC12626, EFC12703)	**Labeling** **SPC Section** *4.3 Contraindications* "Hypersensitivity to the active substance or to any of the excipients listed in section 6.1." **SPC Section** *4.8 Undesirable effects* "Anaphylactic reaction " is listed in ADR table as uncommon *Allergic reactions* "Allergic reactions possibly associated with lixisenatide (such as anaphylactic reaction, angioedema and urticaria) have been reported in 0.4% of lixisenatide patients while possibly associated allergic reactions occurred in less than 0.1% of placebo patients during the main 24-week treatment period. Anaphylactic reactions were reported in 0.2% of the lixisenatide treated patients vs. none in the placebo group. Most of these reported allergic reactions were mild in severity. One case of anaphylactoid reaction was reported during clinical trials with lixisenatide."
Hypoglycemia [when used with a SU or basal insulin]	Routine pharmacovigilance Special attention in PSURs	**Labeling** **SPC Section** *4.2 Posology and method of administration* "When Lyxumia is added to existing therapy of a sulphonylurea or a basal insulin, a reduction in the dose of the sulphonylurea or the basal insulin may be considered to reduce the risk of hypoglycaemia. Lyxumia should not be given in combination with basal insulin and a sulphonylurea due to increased risk of hypoglycaemia." "The use of Lyxumia does not require specific blood glucose monitoring. However, when used in combination with a sulphonylurea or a basal insulin, blood glucose monitoring or blood glucose self- monitoring may become necessary to adjust the doses of the sulphonylurea or the basal insulin." **SPC Section** *4.4 Special warnings and precautions for use* "Patients receiving Lyxumia with a sulphonylurea or with a basal insulin may have an increased risk of hypoglycaemia. Reduction of the dose of the sulphonylurea or the basal insulin may be considered to reduce the risk of hypoglycaemia. Lyxumia should not be given in combination with basal insulin and a sulphonylurea due to increased risk of

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		hypoglycaemia." **SPC Section** *4.7 Effects on ability to drive and use machines* "When used in combination with a sulphonylurea or a basal insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines." **SPC Section** *4.8 Undesirable effects* "Hypoglycaemia (in combination with sulphonylurea and / or a basal insulin)" listed in ADR table as very common "Hypoglycaemia (in combination with metformin alone)" listed in ADR table as common *Hypoglycaemia* "In patients taking Lyxumia in monotherapy, symptomatic hypoglycaemia occurred in 1.7% of lixisenatide treated patients and in 1.6% of placebo treated patients. When Lyxumia is used in combination with metformin alone, symptomatic hypoglycemia was common and occurred in 7.0% of lixisenatide patients and in 4.8% of placebo patients during the entire treatment period." "In patients taking Lyxumia in combination with a sulphonylurea and metformin, symptomatic hypoglycaemia occurred in 22.0% of lixisenatide treated patients and in 18.4% of placebo treated patients during the entire period (3.6% absolute difference). When Lyxumia is used in combination with a basal insulin with or without metformin, symptomatic hypoglycaemia occurred in 42.1% of lixisenatide patients and in 38.9% of placebo patients during the entire treatment period (3.2% absolute difference)." "During the entire treatment period, when Lyxumia was given with a sulphonylurea alone, symptomatic hypoglycaemia occurred in 22.7% of lixisenatide treated patients versus 15.2% with placebo (7.5% absolute difference). When Lyxumia was given with a sulphonylurea and a basal insulin, symptomatic hypoglycaemia occurred in 47.2% of lixisenatide treated patients compared to 21.6% with placebo (25.6% absolute difference)." "Overall, the incidence of severe symptomatic hypoglycaemia was uncommon (0.4% in lixisenatide patients and 0.2% in placebo patients) during the entire treatment period of the Phase III placebo-controlled studies."
Important potential risks		

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Cardiovascular events	Routine pharmacovigilance Special attention in PSURs A cardiovascular study (EFC11319/ELIXA) is ongoing to further assess cardiovascular outcomes in the population of T2DM Further evaluation in ongoing clinical trial (EFC11321)	**Labeling** **SPC Section** *4.8 Undesirable effects* *Heart rate* "In a study in healthy volunteers, a transient rise in heart rate has been observed after administration of lixisenatide 20 mcg. Cardiac arrhythmias particularly tachycardia (0.8% vs <0.1%) and palpitations (1.5% vs 0.8%) have been reported in lixisenatide patients compared to placebo treated patients." **SPC Section** *5.1 Pharmacodynamic properties* *Cardiovascular evaluation* "No increase in mean heart rate in patients with type 2 diabetes was seen in all placebo-controlled phase III studies. Mean systolic and diastolic blood pressure reductions up to 2.1 mmHg and up to 1.5 mmHg respectively were observed in phase III placebo-controlled studies. A meta-analysis of all independently adjudicated cardiovascular events (CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure and coronary revascularization procedure) from 8 phase III placebo-controlled studies which included 2673 type 2 diabetes patients treated with lixisenatide and 1448 patients treated with placebo showed a hazard ratio of 1.03 (95% confidence interval 0.64, 1.66) for lixisenatide versus placebo. The number of events in the clinical studies was low (1.9% in lixisenatide treated patients and 1.8% in placebo treated patients), precluding firm conclusions. The incidence of the individual CV events (lixisenatide vs placebo) was: CV death (0.3% vs 0.3%), non-fatal myocardial infarction (0.4% vs 0.4%), non-fatal stroke (0.7% vs 0.4%), hospitalization for unstable angina (zero vs 0.1%), hospitalization for heart failure (0.1% vs zero), and coronary revascularization procedure (0.7% vs 1.0%)."

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Acute pancreatitis	Routine pharmacovigilance Special attention in PSURs Further evaluation in ongoing clinical trials (EFC11319/ELIXA, EFC11321, EFC12382, EFC12261, EFC12626) Pharmacoepidemiology program proposed: - a retrospective database study to estimate the incidence rates of acute pancreatitis, pancreatic and thyroid cancer among T2DM patients treated by GLP-1 receptor agonists vs other antidiabetics - a patient registry to monitor the occurrences of the same events in lixisenatide-treated patients after launch	**Labeling** **SPC Section** *4.4 Special warnings and precautions for use* "Use of glucagon-like peptide-1 (GLP-1) receptor agonists has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, lixisenatide should be discontinued; if acute pancreatitis is confirmed, lixisenatide should not be restarted. Caution should be exercised in patients with a history of pancreatitis."
Medullary thyroid cancer	Routine pharmacovigilance Special attention in PSURs Further evaluation in ongoing clinical trials (EFC11319/ELIXA, EFC11321) Pharmacoepidemiology program (see acute pancreatitis above)	**Labeling** **SPC Section** *5.3 Preclinical safety data* "In 2-year subcutaneous carcinogenicity studies, non-lethal C-cell thyroid tumors were seen in rats and mice and are considered to be caused by a non-genotoxic GLP 1 receptor-mediated mechanism to which rodents are particularly sensitive. C-cell hyperplasia and adenoma were seen at all doses in rats and a no observed adverse effect level (NOAEL) could be not defined. In mice, these effects occurred at exposure ratio above 9.3-fold when compared to human exposure at the therapeutic dose. No C-cell carcinoma was observed in mice and C cell carcinoma occurred in rats with an exposure ratio relative to exposure at human therapeutic dose of about 900-fold. "
Malignant neoplasm	Routine pharmacovigilance Special attention in PSURs Further evaluation in ongoing clinical trials (EFC11319/ELIXA, EFC11321) Pharmacoepidemiology program for pancreatic cancer (see acute pancreatitis above)	See medullary thyroid cancer above

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Immunogenicity / Neutralization	Routine pharmacovigilance Special attention in PSURs Anti-lixisenatide antibodies further analyzed in ongoing clinical trials (EFC11319/ELIXA, EFC11321, EFC12382)	**Labeling** **SPC Section** *4.8 Undesirable effects* *Immunogenicity* "Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop anti-lixisenatide antibodies following treatment with Lyxumia and, at the end of the main 24-week treatment period in placebo-controlled studies, 69.8 % of lixisenatide patients had a positive antibody status. The percentage of patients who were antibody positive was similar at the end of the entire 76-week treatment period. At the end of the main 24-week treatment period, 32.2% of the patients having a positive antibody status had an antibody concentration above the lower limit of quantification, and at the end of the entire 76-week treatment period, 44.7% of the patients had an antibody concentration above the lower limit of quantification. After stopping the treatment, few antibody positive patients were followed-up for antibody status; the percentage decreased to approximately 90% within 3 months and 30% at 6 months or beyond. The change in HbA1c from baseline was similar regardless of the antibody status (positive or negative). Of lixisenatide-treated patients with HBA1c measurement, 79.3% had either a negative antibody status or an antibody concentration below the lower limit of quantification and the other 20.7% of patients had a quantified antibody concentration. In the subset of patients (5.2%) with the highest antibody concentrations, the mean improvement in HbA1c at Week 24 and at Week 76 was in a clinically relevant range; however there was variability in the glycaemic response and 1.9% had no decrease in HbA1c. The antibody status (positive or negative) is not predictive of the reduction of HbA1c for an individual patient. There was no difference in the overall safety profile in patients regardless of the antibody status with the exception of an increase of the incidence of injection site reactions (4.7% in antibody positive patients compared to 2.5% in antibody negative patients during the entire treatment period). The majority of injection site reactions were mild, regardless of antibody status. There was no cross-reactivity versus either native glucagon or endogenous GLP-1."
Dehydration / Acute renal impairment	Routine pharmacovigilance	**Labeling** **SPC Section** *4.4 Special warnings and precautions for use* "Patients treated with Lyxumia should be advised of the potential risk of dehydration in relation to gastrointestinal adverse reactions and take precautions to avoid fluid depletion."
Off-label use in non-T2DM for weight loss	Routine pharmacovigilance	Lyxumia will be made available by prescription only.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Teratogenicity	Routine pharmacovigilance	**Labeling** **SPC Section** *4.6 Fertility, pregnancy and lactation* *Women of childbearing potential* "Lyxumia is not recommended in women of childbearing potential not using contraception." *Pregnancy* "There are no adequate data from the use of Lyxumia in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Lyxumia should not be used during pregnancy. The use of insulin is recommended instead. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Lyxumia should be discontinued." **SPC Section** *5.3 Preclinical safety data* "Animal studies did not indicate direct harmful effects with respect to male and female fertility in rats." "In embryo-foetal development studies, malformations, growth retardation, ossification retardation and skeletal effects were observed in rats at all doses (5-fold exposure ratio compared to human exposure) and in rabbits at high doses (32-fold exposure ratio compared to human exposure) of lixisenatide. In both species, there was a slight maternal toxicity consisting of low food consumption and reduced body weight. Neonatal growth was reduced in male rats exposed to high doses of lixisenatide during late gestation and lactation, with a slightly increased pup mortality observed."
Important missing information		
Use in pregnant women	Routine pharmacovigilance	See above for teratogenicity
Use in lactating women	Routine pharmacovigilance	**Labeling** **SPC Section** *4.6 Fertility, pregnancy and lactation* *Breast-feeding* "It is unknown if Lyxumia is excreted in human milk. Lyxumia should not be used during breast-feeding."
Use in children and adolescents <18 years	Routine pharmacovigilance Additional activities: paediatric development consisting of 2 clinical studies in children ≥10 years in line with the Paediatric Investigational Plan agreed by the EMA	**Labeling** **SPC Section** *4.2 Posology and method of administration* *Paediatric population* "The safety and efficacy of lixisenatide in children and adolescents less than 18 years of age have not yet been established. No data are available." **SPC Section** *5.1 Pharmacodynamic properties* *Paediatric population* "The European Medicines Agency has deferred the obligation to submit the results of studies with Lyxumia in one or more subsets of the paediatric population in type 2 diabetes mellitus."

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Use in very elderly (≥75 years)	Routine pharmacovigilance An elderly study is planned (EFC12703) Further evaluation in ongoing and planned clinical trials (EFC11319/ELIXA, EFC12382, EFC12261, EFC12626)	**Labeling** **SPC Section** *4.2 Posology and method of administration* "No dose adjustment is required based on age. The clinical experience in patients ≥ 75 years is limited." **SPC Section** *5.2 Pharmacokinetic properties* "Age has no clinically relevant effect on the pharmacokinetics of lixisenatide. In a pharmacokinetic study in elderly non-diabetic subjects, administration of lixisenatide 20 mcg resulted in a mean increase of lixisenatide AUC by 29 % in the elderly population (11 subjects aged 65 to 74 years and 7 subjects aged ≥75 years) compared to 18 subjects aged 18 to 45 years, likely related to reduced renal function in the older age group."
Use in patients with moderate and severe renal impairment (with and without low body weight)	Routine pharmacovigilance Special attention in PSURs Further evaluation in ongoing and planned clinical trials (EFC11319/ELIXA, EFC12382, EFC12261, EFC12626, EFC12703)	**Labeling** **SPC Section** *4.2 Posology and method of administration* *Patients with renal impairment* "No dose adjustment is required for patients with mild renal impairment (creatinine clearance: 50-80 mL/min). There is limited therapeutic experience in patients with moderate renal impairment (creatinine clearance: 30-50 mL/min) and Lyxumia should be used with caution in this population. There is no therapeutic experience in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease and therefore, it is not recommended to use Lyxumia in these populations." **SPC Section** *4.4 Special warnings and precautions for use* *Renal impairment* "There is limited therapeutic experience in patients with moderate renal impairment (creatinine clearance: 30-50 ml/min) and no therapeutic experience in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or end-stage renal disease. Lyxumia should be used with caution in patients with moderate renal impairment. Use is not recommended in patients with severe renal impairment or end-stage renal disease." **SPC Section** *5.2 Pharmacokinetic properties* *Patients with renal impairment* "There were no relevant differences in mean C_{max} and AUC of lixisenatide between subjects with normal renal function and subjects with mild impaired renal function (creatinine clearance calculated by the Cockcroft-Gault formula 50-80 ml/min). In subjects with moderate renal impairment (creatinine clearance 30-50 ml/min) AUC was increased by 24% and in subjects with severe renal impairment (creatinine clearance 15-30 ml/min) AUC was increased by 46%. "

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Long term Clinical Trial (EFC11319/ELIXA) The primary objective of this study is to evaluate cardiovascular outcomes with	Final study report 31

Description	Due date
lixisenatide compared to placebo (composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina) in T2DM patients who experienced an acute coronary syndrome (ACS) event, within 180 days prior to the screening visit	December 2014
Study EFC11321 (Efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus insufficiently controlled by metformin (with or without sulfonylurea): a multicenter, randomized, double-blind, parallel group, placebo-controlled study with 24-week treatment period) Assessment of lixisenatide safety and tolerability and of anti-lixisenatide antibody development are part of the secondary objectives of the study	Final study report to be submitted within 1 month of Commission Decision
Study EFC12261(24-week, open-label, randomized, 2-arm parallel group, multinational, multicenter clinical trial to compare the efficacy and safety of lixisenatide injected prior to the main meal of the day versus lixisenatide injected prior to breakfast in type 2 diabetic patients not adequately controlled on metformin) Assessment of safety and tolerability of both lixisenatide regimens are part of the secondary objectives of the study.	Final study report 31 December 2013
Study EFC12382 (A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week treatment period assessing the efficacy and safety of lixisenatide in patients with type 2 diabetes insufficiently controlled with basal insulin with or without metformin) Assessment of lixisenatide safety and tolerability and of anti-lixisenatide antibody development are part of the secondary objectives of the study.	Final study report 31 December 2015
Study EFC12626 (A randomized, open-label, active-controlled, 3-arm parallel-group, 26-week study comparing the efficacy and safety of lixisenatide to that of insulin glulisine once daily (Basal Plus regimen) and insulin glulisine three times daily (Basal Bolus regimen) in patients with type 2 diabetes insufficiently controlled with insulin glargine with or without metformin) Assessment of safety and tolerability of both lixisenatide regimens are part of the secondary objectives of the study, in particular on: incidence and events rates of documented (PG <60 mg/dl) symptomatic hypoglycemia and severe hypoglycemia.	Final study report 31 March 2015
Study EFC12703 (A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter, 24-week study assessing the safety and efficacy of lixisenatide in older patients with type 2 diabetes inadequately controlled on their current diabetes treatment regimen). The objectives of this study are to collect additional safety and efficacy data in patients of 70 years of age or older.	Study protocol to be submitted within 3 months of Commission Decision, Final study results 30 June 2015
A retrospective database study using the existing databases and registries in Sweden, Denmark, and Norway. Primary objective: to estimate the incidence rates of acute pancreatitis, pancreatic and thyroid cancer among adult T2DM patients treated with GLP-1 receptor agonists (i.e., exenatide & liraglutide) versus the ones treated with other anti-diabetics Secondary objective: to evaluate the potential association between acute pancreatitis, pancreatic cancer and thyroid cancer, in particular medullary	Study protocols to be submitted within 6 months of Commission Decision, together with proposed

Description	Due date
carcinoma of the thyroid and the use of treated with GLP-1 receptor agonists versus other anti-diabetics among adult T2DM patients.	timelines.
A patient registry including adult T2DM patients treated with lixisenatide after launch in Sweden, Denmark, and Norway. To monitor the occurrences of events of interest including acute pancreatitis, pancreatic and thyroid cancer among adult T2DM patients treated with lixisenatide after launch	Study protocols to be submitted within 6 months of Commission Decision, together with proposed timelines.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Patients with type 2 diabetes are at increased risk of macro- and microvascular complications including cardiovascular morbidity and mortality. A major purpose of using antidiabetic agents is to reduce these risks. HbA1c is generally accepted as surrogate marker for treatment effect and was included as the primary endpoint in the pivotal studies. Other important endpoints in studies of patients with type 2 diabetes, such as changes in body weight and fasting glucose, were included as secondary endpoints.

A study to estimate the effect size of lixisenatide as monotherapy showed a placebo-adjusted reduction of HbA1c of approximately 0.6% after 12 weeks treatment. The mean change in body weight was very similar in the placebo and the active group (approx. 2 kg reduction).

In the two placebo-controlled add-on to metformin studies, treatment with lixisenatide resulted in statistically significant reductions in HbA1c compared to placebo ranging from 0.37 to 0.49 %. Mean reductions in body weight were small and the difference compared to placebo was statistically significant in one of the two studies.

The results in study EFC6017, in which lixisenatide was added to pioglitazone +/- metformin, showed a similar placebo-corrected reduction of HbA1c of -0.56%.

As add on to SU, or SU+metformin, the mean placebo corrected reduction of HbA1c was 0.74 %. Mean reduction in body weight was 1.7 kg in the lixisenatide group. The difference compared to placebo was statistically significant.

Two studies examined the additive effect of lixisenatide when added to ongoing insulin treatment with or without metformin (EFC6016) or SU (EFC10887). In study EFC6016, the placebo-corrected reduction of HbA1c (-0.36%) was statistically significant. Mean body weight was reduced by 1.80 kg in the lixisenatide group. Study EFC10887 was entirely performed in Asia and in this study the placebo

adjusted reduction in HbA1c was 0.88%, but the effect on body weight was very limited. The insulin doses in these studies did not change much in the placebo or lixisenatide groups (in accordance with study designs). During the procedure, results from an additional study (EFC 10781) were submitted in which lixisenatide was added to insulin glargine and OAD. The benefit (with respect to HbA1c) of adding lixisenatide in comparison to up-titration of the insulin glargine dose in study EFC10781 was -0.32%. The benefit with respect to body weight was a -0.9 kg difference compared to placebo.

In the active controlled study EFC6019, the reduction of HbA1c with exenatide was 0.96% compared to 0.79% with lixisenatide (mean difference 0.17%, upper 95% CI of 0.297% in the pre-defined mITT population and 0.315% in the completer population). The reduction in body weight for exenatide and lixisenatide were -3.98 kg and -2.96 kg, respectively.

The glucose-lowering effect of lixisenatide was in general maintained in patients who continued into the extension phases of the studies.

The effect of lixisenatide on plasma glucose parameters was significantly larger compared to placebo in all studies. In one phase 2 study, lixisenatide was more effective than liraglutide in lowering post prandial glucose after 28 days of treatment.

Uncertainty in the knowledge about the beneficial effects

The results of the phase 3 studies show a difference in glucose lowering effect between Asian and Caucasian patients, with larger reductions of HbA1c in Asian patients (e.g. study EFC6015 and EFC10887). This was further examined in the phase 2 study PDY6797. Also in this study, the effect of lixisenatide was more pronounced in Japanese patients compared to Caucasians and the treatment-by-ethnicity interaction test was statistically significant. This may be explained by the fact that Japanese patients had a lower BMI and higher insulin sensitivity at baseline. Japanese patients also had higher concentrations of lixisenatide which in turn was likely due to the lower mean body weight. The lower effect in Caucasians is partly explained by a large placebo effect especially in some geographical regions. In further analyses of patients recruited in Western and Eastern Europe, the mean placebo corrected effect was a reduction of HbA1c of about 0.5 % and a weight reduction of about 1kg.

The assessment of the effect of lixisenatide as add on to insulin (with and without metformin) was hampered by the large placebo effect in two of the submitted studies. Based on subgroup analyses of patients who could be expected to be adherent to background therapy, a reduction of HbA1c of 0.5-0.6% compared to placebo was considered as plausible which is of clinical relevance. Further, responder rates showed an additive effect compared to placebo.

The number of patients above the age of 75 or with moderate and severe renal impairment is very limited.

Pooled analyses of anti-lixisenatide antibody status showed that at the end of the main treatment period (Week 24), 69.4% of evaluable patients were assessed as antibody-positive. For those with the highest antibody concentrations, the mean HbA1c reducing effect was attenuated. However, overall, no correlation between antibody concentration categories and change in HbA1c was seen and therefore antibody status cannot be used as a predictor of the glucose lowering effect of lixisenatide.

Risks

Unfavourable effects

The most common short-term safety issue are gastrointestinal side effects. Nausea (26%) and vomiting (10.5%) and diarrhoea (8.3%) were mostly mild to moderate in intensity and new events

peaked within the first 3 weeks and thereafter decreased. Approximately 70-80% of the patients experiencing nausea and/or vomiting completed the treatment. The labelling includes a recommendation concerning a gradual up-titration of the dose to reduce these symptoms. In the active controlled study versus exenatide (EFC6019), the incidence rate of nausea was 24.5% in the lixisenatide groupcompared to 35.1% for exenatide.

In all controlled studies in the Phase 2/3 pool, the incidence of injection site reaction was 5.3% in the lixisenatide group and 1.9% in the all comparator group (placebo + active). In the main treatment period of the Phase 3 placebo-controlled studies, the incidence of injection site reaction was 3.9% in the lixisenatide group and 1.4% in the placebo group. In the comparative study with exenatide, the incidence of injection site reactions was 9.1 and 2.2% for lixisenatide and exenatide, respectively.

For the lixisenatide treated patients, approximately 70 % had a positive antibody status at the end of the main 24-week treatment period and throughout the entire 76-week treatment period in placebo-controlled studies. After stopping the treatment, antibody concentration decreased over time. However, the majority of the patients (67%) who discontinued were still positive after 3-6 months.

Patients positive for anti-lixisenatide antibodies were at higher risk for developing injection site reactions compared with those without antibodies. There were no differences for other adverse events.

Allergic reactions possibly associated with lixisenatide were reported in 0.4% of lixisenatide patients compared with less than 0.1% of placebo patients during the main 24-week treatment period in phase 3 studies. Anaphylactic reaction was observed in 8 patients in the lixisenatide group (0.2%) vs none in the all-comparator group (0%). A positive allergic history was reported for 3 of the patients. Three events were reported in patients with negative antibody status or concentration < LLOQ, 1 in a patient with a positive antibody status but no evaluation of antibody concentration, and 3 events were reported in patients with antibody concentration > 15.50 nmol/L.

Hypoglycaemia is mainly seen when lixisenatide treatment is combined with SU and/or insulin. The product information states that when lixisenatide is added to SU therapy or basal insulin a reduction of dose of the SU or the basal insulin may be considered to reduce the risk of hypoglycaemia. The hypoglycaemia rate in combination with sulfonylurea and insulin is more than doubled compared to placebo.The use of lixisenatide in this triple combination is advised against in section 4.2 of the SmPC and a warning to that regard is included in section 4.4.

Uncertainty in the knowledge about the unfavourable effects

The meta-analysis of CV events (MACE; CV death, non fatal myocardial infarction and stroke) resulted in a point estimate above one (HR 1.25, 95% confidence interval 0.67-2.35). However, the cases were very few and the difference did not reach statistical significance which is a limitation of these results. The increase in MACE was driven by a difference in non fatal stroke (0.7% versus 0.4% for placebo). The incidence of other MACE endpoints did not differ between lixisenatide and placebo.

Lixisenatide treatment was associated with a higher incidence of palpitations compared to placebo (1.5% vs 0.6% for placebo) as well as tachycardia (0.7% vs <0.1% for placebo). In addition, supraventricular arrhythmias (1.1% versus 0.7%) and cardiac conduction disorders (0.6% versus 0.1%) were increased for lixisenatide treated patients compared to placebo patients. There is no indication of QT prolongation in study TES11807, although an increased heart rate (+7.3 bpm) approximately 1 hour after dosing was seen in the QT study in healthy volunteers, an observation made also with other products of the same class. In the phase 3 studies no mean increase in heart rate or blood pressure was noted.

Due to potential signals of hypospermatogenesis identified from toxicology studies in dogs, the potential for similar changes with lixisenatide in healthy humans was investigated in Study TDR11215. The results for the primary endpoint did not indicate a statistically significant difference compared to placebo with respect to proportion of subjects with at least 50% reduction in sperm concentration. The data provided for the other important secondary endpoints sperm parameters, i.e. sperm count, sperm motility and sperm morphology, were reassuring.

A very low number of patients with moderate renal impairment were included in phase 3 studies. The data is scarce and it is difficult to draw any firm conclusions from the reported safety data. Given the signal of a slight increase in adverse events in mild renal impairment and very limited clinical experience in moderate renal impairment, the SmPC recommends use with caution in patients with moderate renal impairment. There is no therapeutic experience in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or end-stage renal disease and therefore in the SmPC it is not recommended to use lixisenatide in these populations.

As for other GLP 1 agonists, the clinical relevance of the thyroid C cell tumours in rats cannot be excluded. In the clinical development program there is no indication of trends in the incidences of thyroid neoplasms. This will be followed in post authorisation studies.

Pancreatic carcinoma was reported by 3 (<0.1%) lixisenatide patients and 1 (<0.1%) patient in the comparator group. Thus, no trends could be observed.

In the developmental toxicity studies there were a number of malformations and a relation to treatment cannot be excluded, and therefore, as a precaution, lixisenatide is not recommended in women of child bearing potential not using contraception in the SmPC.

Benefit-risk balance

Importance of favourable and unfavourable effects

Treatment with lixisenatide as add on to other glucose lowering therapies resulted in absolute reductions in HbA1c of -0.74 to - 0.92% (12-24 weeks of treatment). The placebo adjusted reductions ranged from -0.36 to -0.88% thus demonstrating improved glycaemic control. This magnitude of glucose lowering effect is considered as clinically relevant and is expected to reduce the risk of micro- (and potentially macro-) vascular complications. The mean difference in body weight compared to placebo was approximately 1 kg. In the diabetic population, reduction of body weight is always of clinical relevance and advantageous compared to the increase in weight with some other therapeutic options.

Concerning non-inferiority compared to exenatide, this has not been robustly shown with respect to reduction of HbA1c and weight reduction. However, there are benefits compared to exenatide such as once daily dosing and a lower incidence of nausea and hypoglycaemia. Therefore, a possibly lower effect is considered as acceptable, especially considering that the reduction of HbA1c with lixisenatide in the comparative study was of clear clinical relevance (-0.79% reduction) as was the reduction of body weight (-2.8 kg).

With regard to safety, as for other GLP-1 analogues, gastrointestinal adverse events are most common. The incidence declines with time and rarely leads to treatment discontinuation.

The meta-analysis of major cardiovascular events (MACE) resulted in a HR of 1.25 (95% confidence interval 0.67-2.35). However, the cases were very few and the difference did not reach statistical significance which is a limitation of these results. The increase in MACE was driven by a difference in non fatal stroke while the incidence of other MACE endpoints did not differ between lixisenatide and

placebo. Therefore, the available data is not considered to show an increased risk of MACE associated with lixisenatide.

The slightly increased incidence of palpitations and tachycardia compared to placebo as well as the findings of a transient increase in heart rate in healthy volunteers indicate a propensity of lixisenatide to increase heart rate. However, there was no mean increase in heart rate in the clinical studies and no increase in blood pressure. Further, not only lixisenatide but also other GLP-1 receptor agonists have been associated with a trend to increased heart rate and based on available data, there is no indication that the effect is more pronounced with lixisenatide compared to other products in the class. More information with regard to CV effects will be obtained in the ongoing CV outcome study (long term clinical trial EFC11319/ELIXA).

The proportion of patients developing antibodies to lixisenatide was high. However, the only adverse events being more common in patients with antibodies are injection site reactions, an association which has also been reported for other products in the class. Further, the incidence of allergic reactions possibly associated with lixisenatide was low (0.4%) and the anaphylactic reactions reported were mostly low grade in severity. Hypersensitivity reactions are continued to be reviewed and adjudicated in ongoing trials.

Due to findings in the developmental toxicity studies, a teratogenic potential of lixisenatide cannot totally be excluded. Maternal effects on body weight and food consumption can result in foetal effects which have been shown with other members of the class. Given that such effects on body weight and food consumption are not observed clinically, the relevance for humans would be minimal. However, the applicant has not been able to demonstrate that the malformations in the lixisenatide studies are completely explained by such maternal effects. Therefore, as a precaution, lixisenatide is not recommended in women of child bearing potential not using contraception. The SmPC contains this information accordingly, and teratogenicity is included as a potential risk in the RMP.

Benefit-risk balance

The absolute glucose-lowering effect of lixisenatide with a weight reducing effect at the same time is considered to be a clinical relevant benefit. The safety profile is largely similar to other products in the class with gastrointestinal adverse events being most common. There are potential risks associated with a propensity to induce increased heart rate, pancreatitis and allergic reactions, which will be followed in post marketing studies, as well as uncertainties with respect to embryofoetal toxicity, which is managed by the restriction that Lyxumia is not recommended in women of childbearing potential not using contraception. These risks are considered to be outweighed by the shown benefits.

Discussion on the benefit-risk balance

The B/R of Lyxumia is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Lyxumia in the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that lixisenatide is qualified as a new active substance.