10 November 2016
EMA/800280/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Suliqua

International non-proprietary name: insulin glargine / lixisenatide

Procedure No. EMEA/H/C/004243/0000

Note

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

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Administrative information

Name of the medicinal product:	Suliqua
Applicant:	sanofi-aventis groupe 54 rue La Boetie 75008 Paris FRANCE
Active substance:	insulin glargine / lixisenatide
International Non-proprietary Name/Common Name:	insulin glargine / lixisenatide
Pharmaco-therapeutic group (ATC Code):	Drugs used in diabetes, insulins and analogues for injection, long-acting A10AE54.
Therapeutic indication(s):	Suliqua is indicated in combination with metformin for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin (see section 4.4 and 5.1 for available data on the different combinations).
Pharmaceutical form(s):	Solution for injection
Strength(s):	100 U/ml / 33 µg/ml and 100 U/ml / 50 µg/ml
Route(s) of administration:	Subcutaneous use
Packaging:	cartridge (glass) in a pre-filled pen
Package size(s):	3 pre-filled pens and 5 pre-filled pens

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List of abbreviations

AA:	amino acids
AAS:	atomic absorption spectrometry
ADA/EASD:	American Diabetes Association/European Association for the Study of Diabetes
ANCOVA:	analysis of covariance
ARAC:	allergic reaction assessment committee
BMI:	body mass index
CAC:	cardiovascular assessment committee
CD:	Circular dichroism
Cfu:	colony forming unit
CI:	confidence interval
CRF:	case report form
CV:	cardiovascular
E. coli:	*Escherichia coli*
eCRF:	electronic case report form
ELISA	enzyme linked immunosorbent assay
FPG:	fasting plasma glucose
FRC:	fixed-ratio combination
GC:	gas chromatography
GC-MS	gas chromatography with mass spectrometry detection
GI:	gastrointestinal
GIR-AUC_{0-24h}:	area under the concentration-time curve for the glucose infusion rate from zero to 24 hours
GLP-1:	glucagon like peptide-1
HbA1c:	glycated haemoglobin
HPLC:	High Performance Liquid Chromatography
HPSEC:	High Pressure Size Exclusion Chromatography
ILA:	Immunoligand assay
IMP:	investigational medicinal product
ISS:	integrated summary of safety
KF:	Karl Fischer
MCB:	master cell bank
MIB:	Multi-Insulin Building
mITT:	modified intent-to-treat
MMRM:	mixed-effect model with repeated measures
MS:	Mass spectrometry
MTD:	maximum tolerated dose
NMR:	Nuclear Magnetic Resonance
NOR:	Normal Operating Range
OAD:	oral antidiabetic drug
PAGE	polyacrylamide gel electrophoresis
PCSA:	potentially clinically significant abnormalities
PG:	plasma glucose
PK:	pharmacokinetic
PPG:	postprandial plasma glucose
PRE:	pen-related event
PSAC:	pancreatic safety assessment committee
PY:	patient-years

QD:	once daily
SAE:	serious adverse event
SAP:	statistical analysis plan
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SEC-HPLC	Size-exclusion chromatography-High Performance Liquid Chromatography
SMPG:	self-monitored plasma glucose
TAMC:	total aerobic microbial count
T1DM:	type 1 diabetes mellitus
T2DM:	type 2 diabetes mellitus
ULN:	upper limit of normal
TTC:	threshold of toxicological concern
TYMC:	total yeasts/moulds count
WCB:	working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi-aventis groupe submitted on 3 March 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Suliqua, 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 25 June 2015.

The applicant applied for the following indication:

Suliqua is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with basal insulin, or basal insulin alone do not provide adequate glycaemic control (see section 5.1 for available data on the different combinations).

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

The application submitted is

a new fixed dose combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/168/2010 on the granting of a (product-specific) waiver.

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.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 March 2010. The Scientific Advice pertained to insert quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Bart Van der Schueren

- The application was received by the EMA on 3 March 2016.
- The procedure started on 24 March 2016.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2016 (Annex 1).
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2016 (Annex 2).
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 June 2016 (Annex 3).
- During the meeting on 21 July 2016, 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 25 July 2016 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 26 September 2016 (Annex 5).
- During the PRAC meeting on 29 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP (Annex 6).
- During the CHMP meeting on 13 October 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 7).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 October 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 26 October 2016 (Annex 8).
- During the meeting on 10 November 2016, 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 Suliqua.

2. Scientific discussion

2.1. Problem statement

Type 2 diabetes mellitus is characterized by a gradual deterioration in β cell function; this occurs even when standard-of-care antidiabetic therapy is used, including concurrent use of multiple oral antidiabetic drugs (OADs). Since T2DM is phenotypically heterogeneous, e.g., race/ethnicity, age at onset, duration of disease, body weight, comorbidities, and deficits in fasting versus postprandial hyperglycaemia, these phenotypic variables significantly influence the choice of anti-hyperglycaemic therapy. In the last decade, several new therapeutic classes have become available, enabling a patient-centred rather than one-size-fits-all approach and moving T2DM management towards appropriate dual therapy at an earlier point in the disease continuum.

The timely introduction of basal insulin to intensify treatment in patients with T2DM insufficiently controlled on OADs has been recommended by the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) since 2006. Although metformin remains the consensus first-line drug in newly diagnosed patients without symptoms of significant hyperglycaemia, GLP-1 receptor agonists are recommended as part of metformin-based dual and triple therapy after failure of metformin monotherapy per the ADA/EASD 2015 position statement.

For patients insufficiently controlled on one or more OADs, initiation of insulin treatment is often delayed due to clinical inertia. In a retrospective study published in 2014 of more than 50 000 patients with T2DM in the United States, 4 out of 5 patients not achieving glycaemic control on dual oral therapy were prescribed another OAD rather than insulin. Another recent retrospective cohort study followed more than 80 000 patients with T2DM up to 2011; maximum follow-up was 7.3 years. The median time to insulin intensification in patients with HbA1c ≥7.0% taking 2 or 3 OADs was >7 years. Physician reluctance to initiate insulin therapy, often due to concerns about hypoglycaemia and weight gain, thus contributes to prolonged periods of sustained hyperglycaemia.

Patients with insufficiently controlled T2DM already on basal insulin represent an additional unmet need. Dual therapy with a GLP-1 receptor agonist and basal insulin (injected separately), based on the original findings reported for exenatide by Buse et al (2011) and recently confirmed for lixisenatide, has been added as an antidiabetic treatment option. The 2015 ADA/EASD T2DM position statement recommends that if glucose control remains poor despite the use of basal insulin with one or more oral agents, either a GLP-1 receptor agonist or prandial insulin can be added. The guideline states further that “The available data now suggest that either a GLP-1 receptor agonist or prandial insulin could be used in this setting, with the former arguably safer, at least for short-term outcomes. The addition of a GLP-1 receptor agonist or mealtime insulin could be viewed as a logical progression of the treatment regimen, the former perhaps a more attractive option in more obese individuals or in those who may not have the capacity to handle the complexities of a multi-dose insulin regimen.”

The fixed-ratio combination (FRC) of insulin glargine (100 U/mL) with lixisenatide is intended for the treatment of adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with basal insulin, or basal insulin alone do not provide adequate glycaemic control.

The fixed-ratio combination is intended to be administered subcutaneously once a day within 1 hour prior to any meal of the day.

The FRC could provide a benefit to patients since simultaneous once-daily injection of a dual anti-hyperglycaemic therapy may improve treatment compliance. This in turn could allow more patients to

reach glycaemic goals without increasing safety or tolerability risks. The FRC is appropriate both for patients beginning insulin-based treatment and those already on established basal insulin.

The development program includes two pivotal phase III studies which include a total of 1906 patients with T2DM. Both studies were of 30 weeks duration.

The development program is in all essentials in line with the Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1).

Suliqua is a fixed ratio combination between the basal insulin glargine and the glucagon-like peptide-1 (GLP-1) analogue lixisenatide. Both individual components have been approved previously in the EU, insulin glargine as Lantus (2000) and lixisenatide as Lyxumia (2013). Suliqua is available as solution for injection and provided in two different prefilled pens with constant ratios between the two substances (the 10-40 pen with a ratio of 2U insulin glargine/1 µg lixisenatide and the 30-60 pen with a ratio of 3U insulin glargine/1 µg lixisenatide). It is intended to be used for once-daily parenteral administration.

2.2. Quality aspects

2.2.1. Introduction

The finished product Suliqua is a fixed ratio combination (FRC) consisting of insulin glargine and lixisenatide, being proposed for the treatment of adults with type 2 diabetes mellitus.

The finished product is presented as an aqueous, sterile, clear and colourless solution containing 100 units/ml of insulin glargine and lixisenatide (50 microgram/ml or 33 microgram/ml) as active substances, for once-daily subcutaneous injection. The finished product is available in a Type I colourless glass cartridge with a black plunger (bromobutyl rubber) and a flanged cap (aluminium) with inserted laminated sealing disks (bromobutyl rubber on the medicinal product side and polyisoprene on the outside) containing 3 mL of solution. Each cartridge is assembled into a disposable pen. The pen-injector is designed to deliver multiple doses of variable volume and was based on the already marketed SoloStar® pen-injector.

To maximize the range of insulin glargine and concomitantly deliver lixisenatide to approximate its maximum clinical dose, two different strengths have been developed (2 different dose ratios):

- 10-40 prefilled pen: solution for injection containing 100 U/ml insulin glargine and 50 mcg/ml lixisenatide (ratio of 2 U insulin glargine/1 mcg lixisenatide). The pen delivers doses from 10 to 40 U in steps of 1 unit, allowing administration of FRC doses between 10 U/5 mcg and 40 U/20 mcg.
- 30-60 prefilled pen solution for injection containing 100 U/ml insulin glargine and 33 mcg/ml lixisenatide (ratio of 3 U insulin glargine/1 mcg lixisenatide). The pen delivers doses from 30 to 60 U in steps of 1 unit, allowing administration of FRC doses between 30 U/10 mcg and 60 U/20 mcg.

The caps and bodies of the two strengths of the insulin glargine / lixisenatide pen-injectors feature different colors: peach for pen A and olive for pen B. In addition, the injection buttons of both pens are also colored differently: orange (pen A) and dark orange (pen B). Apart from colors and mechanical parts pertaining to different dose strengths, the overall geometry and function of each pen variant is identical.

Figure 1 - Insulin glargine / lixisenatide pen-injectors with different colours

10-40 prefilled pen

30-60 prefilled pen

2.2.2. Active Substance

Both active substances are already approved as part of mono-component centralised marketing authorisations; Lantus (insulin glargine) held by Sanofi-Aventis Deutschland GmbH, and Lyxumia (lixisenatide) held by sanofi-aventis groupe. The active substance manufacturing processes and controls presented for Suliqua are in line with those approved for the mono-component products. Further detail is elaborated below.

General Information

The active substance insulin glargine is a human insulin analogue produced by means of recombinant DNA technology in *E. coli*. It is a protein consisting of 2 chains: the A-chain containing 21 amino acids and the B-chain containing 32 amino acids. In comparison to insulin human, asparagine is substituted by glycine at the C-terminal end of the A-chain and two arginines are added to the C-terminal end of the B-chain. The A- and B-chains are linked by 2 interchain disulfide bonds and the A-chain contains one intrachain disulfide bond. There are no other post-translational modifications.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Insulin glargine is produced by recombinant DNA technology in *E. coli* as a fusion protein containing a pre-sequence (to protect against proteolytic degradation) and the pro-insulin sequence from a primate which is modified resulting in insulin glargine.

The insulin glargine active substance manufacturing process has been adequately described. The main steps are fermentation, recovery, purification, crystallisation and drying. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria are described for each step. The active substance manufacturing process is considered acceptable.

The manufacturing process of the active substance comprises a number of steps in which the protein is expressed in *E. coli* bacteria (pre-fermentation and main fermentation), recovered (disruption of cells and inclusion bodies, isolation of fusion protein by continuous centrifugation, folding and precipitation of by-products, tryptic cleavage of prepro-sequence from fusion protein), purified (various purification and chromatographic steps), crystallised and dried.

The in-process controls include parameters and limits for fermentation in the upstream process (such as pressure, aeration, oxygen pressure, pH, glucose concentration, temperature, stirring, total weight) and for purification steps in the downstream process (such as content of insulin glargine and by-products and step

yields). These were considered acceptable based on the results from manufacturing development/experience and process validation provided by the applicant.

A seeding culture is prepared by inoculation with one ampoule of the working seed bank and transferred to the first bioreactor with medium for amplification. The material from this pre-fermentation step is transferred into the next bioreactor with medium for the main fermentation, including the production phase. At the end of fermentation, the cells are inactivated and then separated for the following isolation of fusion protein. Thus material from a single ampoule is amplified and processed to give one harvest of cells with fusion protein.

Usually, the harvest from one fermentation run is processed downstream to give one batch of insulin glargine. Samples are taken and the product is filled into containers of stainless steel, which are immediately labelled and transferred to the freezing room for storage at -20°C ± 5°C.

This manufacturing process takes place at Sanofi-Aventis Deutschland GmbH in Germany in two facilities (i.e. the so-called Lantus Plant and Multi-Insulin Building (MIB) facilities) and is well defined and overall considered adequately controlled.

Control of materials

Sufficiently detailed information is provided on the raw materials used for the production of insulin glargine. No antibiotics or human/animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate. The host cell strain *E. coli* K12 has been thoroughly characterised with regard to physiological tests, bacteriophage test, ELISA and genetic tests.

A two tiered cell banking system is used and sufficient information is provided regarding testing of MCB and WCB and release of future WCBs. Both the MCB and two WCBs are fully characterised in accordance with ICH Q5B and Q5D guidelines with regard to identity, phenotypic characteristics, growth characteristics, viable cell count, plasmid identity, plasmid retention, plasmid copy number, expression of fusion protein, verification of coding sequence, microbial contamination.

In addition, genetic stability for end of production cells has been verified through extended fermentation runs at final production scale. Genetic and storage stability of the production cell line has been addressed for the MCB and first WCB.

Control of critical steps and intermediates

Adequate limits are set for the in-process controls by which correct performance of fermentation is confirmed. The fusion protein isolated from the cell paste, is enriched by re-suspension and centrifugation steps and then combined with cysteine which prevents the growth of potential microbial contaminants. Downstream processing of the fusion protein to insulin glargine is a sequence of modification and efficient purification steps. Each intermediate is enriched or purified to a quality which is suitable for the next step.

A full description of the in-process controls (IPCs) is provided in Section 3.2.S.2.4 Control of critical steps and intermediates, including an overview for the critical process parameters and the in-process controls for each step of the manufacturing process, together with acceptance criteria and justifications.

Several intermediates are formed during the manufacturing process, for which normal and maximal storage periods are defined. Supporting validation data to substantiate these storage claims for all intermediates are provided.

Process validation

Process validation data are presented for consecutive production scale batches. The results from the process and product parameters controlled, together with process development history and experience, and batch release results demonstrate that the established manufacturing process is capable of yielding a product of appropriate quality. In addition, the purification process shows a good consistency in the elimination of both process-related and product-related impurities.

Manufacturing process development

The manufacturing process development is described in detail from the beginning of development up to the latest changes introduced. Each step of the manufacturing process has been thoroughly discussed with regard to the establishment and optimization of all process and/or product parameters involved in order to yield a product of high (or increased) quality. All batches used in clinical studies, non-clinical studies, development, pilot and production scale manufacturing have been stated in clear overviews. All results complied with the acceptance criteria and batches manufactured revealed no significant difference. The quality of insulin glargine active substance manufactured at both facilities is thus guaranteed.

Characterisation

The insulin glargine active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods. The analytical results are consistent with the proposed structure. The methods addressed the molecular mass, primary structure, secondary and tertiary structures, crystal structure and several physicochemical parameters, i.e. isoelectric point, solubility in aqueous medium, influence of pH on structure and effect of zinc concentration on hexamer formation. The absence of a potency assay was acceptable as the active substance is well characterised and already approved as part of the centralised product, Lantus. Overall, a detailed and sufficient characterisation of the active substance has been made. With regard to the product- and process-related impurities, these are considered sufficiently addressed and controlled.

Specification

Specifications have been established for insulin glargine and are considered appropriate to ensure sufficient quality with regard to appearance, identity, purity/impurities, quantity, microbiological quality and endotoxins. There were no changes made to the proposed specification during the procedure. The acceptance limits are in compliance with the Ph. Eur. monograph 2571 for insulin glargine.

Analytical Methods

All the analytical methods used are those published in the Ph. Eur. monograph of insulin glargine (current edition) except the ILA for the quantification of *E. coli* proteins, which is sufficiently described. The test methods chosen are considered acceptable. Additionally, validation data are supplemented for the test for microbiological content and bacterial endotoxins according to Ph. Eur. requirements.

Batch Analysis

The specifications are justified based on batch analysis data of 10 release batches and 3 stability batches. The results are within the specifications and confirm consistency of the manufacturing process.

Reference Materials

The compendial insulin glargine reference standard is applied for testing the active substance batches. An insulin glargine active substance batch can be calibrated as secondary reference standard against the compendial standard. Qualification of such a batch is performed according to the control tests and specifications for the

active substance. In addition, calibration against the official compendial standards is performed periodically. An overview of the reference batches used to date is also provided.

Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life of 24 months stored in an airtight container (steel drum), protected from light, at a temperature between -25 °C and -15 °C.

Stability results from 3 batches stored under long term (-20 °C ± 5 °C) and accelerated (+5 °C ± 3 °C) storage conditions show a good stability profile for the active substance. All parameters remained stable over time except for a slight increase in water content. The representativeness of the container closure system used during stability studies compared to the one used in routine production and storage is demonstrated in a comparative stability study of primary packaging material. The suitability of the primary packaging material for the active substance insulin glargine is considered demonstrated. In addition, it is acknowledged that the smaller volume containers represent worst case conditions with respect to product-container contact. An ICH Q1B photostability study revealed that insulin glargine is sensitive to light exposure.

The claimed shelf-life period of 24 months for the active substance insulin glargine at the recommended storage conditions (i.e. store in an airtight container, protected from light, at a temperature between -25 °C and -15 °C) is supported.

LIXISENATIDE

An ASMF procedure is used for the active substance lixisenatide. The documentation provided in this Suliqua application is identical to that currently approved for Lyxumia.

General Information

Lixisenatide is a peptide containing 44 amino acids, which is amidated at the C-terminal AA (position 44). 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.

It is white to off-white amorphous powder, freely soluble in water and hygroscopic. Lixisenatide is photosensitive, when exposed to intensive light.

Manufacture, characterisation and process controls

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 includes the following tests and acceptance criteria to assure consistent quality of the active substance: 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), Chiral purity (AAA-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.

The analytical methods used are fully described. The methods are validated and they are suitable for their intend use.

Batch analysis data (22 of batches, including 3 production scale) of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Information regarding the reference standards used for assay and impurities testing has been presented, together with certificates of analysis of reference materials for the related substances used in the validation of the analytical methods.

Lixisenatide active substance is packed into amber glass bottles with airtight closing screw caps. Due to its sensitivity to light, lixisenatide has to be protected from light. This is assured by the primary packaging. The packaging 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 specifications of the components are provided.

Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed retest period of 60 months when stored at -20°C ±5°C in the proposed container.

Stability data are available for 3 stability commercial scale batches of active substance from the commercial manufacturing process through 60 months of storage at -20°C±5°C in the intended container. In addition, stability data are also available for 3 production batches of active substance from the commercial manufacturing

process through 48 months of storage for 2 batches and 60 months of storage for one batch at -20°C±5°C in the intended container.

The following parameters were tested:

- Appearance of the drug substance (visual)
- Assay lixisenatide (HPLC 1)
- Related impurities 1 (HPLC 1)
- High molecular weight proteins (HPSEC)
- Water content (Karl Fischer).

The analytical methods used were the same as for release and were stability indicating. The test results demonstrate the adherence to the limits of the stability-relevant control tests. All results are in compliance with the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch. The photostability studies showed that lixisenatide is photosensitive when exposed to intense light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months when stored at -20°C ±5°C in the proposed container.

2.2.3. Finished Medicinal Product

Description of product and Pharmaceutical development

Suliqua is an aqueous, sterile, clear and colourless solution for once-daily subcutaneous injection. The finished product contains insulin glargine and lixisenatide and the following excipients: glycerol, methionine, metacresol, zinc chloride, hydrochloric acid, sodium hydroxide and water for injection.

The finished product is available in two strengths;

- 3.64 mg/mL insulin glargine [equivalent to 100 U of insulin glargine] with 50 mcg/mL lixisenatide
- 3.64 mg/mL insulin glargine [equivalent to 100 U of insulin glargine] with 33 mcg/mL lixisenatide.

All excipients are well known pharmaceutical ingredients and their quality complies with Ph.Eur. standards. There are no novel excipients used in the finished product formulation.

It is packed in Type I colourless glass cartridges with a black plunger (bromobutyl rubber) and a flanged cap (aluminium) with inserted laminated sealing disks (bromobutyl rubber on the medicinal product side and polyisoprene on the outside) containing 3 mL of solution. Closures comply with Ph. Eur.The cartridge is irreversibly integrated in a disposable mechanical pen-injector for self-administration by the patient. The pen-injector is designed to deliver multiple doses of variable volume and was based on the already marketed SoloStar® pen-injector, which is approved as part of the mono-component insulin glargine product, Lantus. Each dose strength has its own pen-injector of different colour, which is deemed suitable to avoid confusion. The pens and cartridges were investigated with respect to performance according to the applicable ISO standards and passed all criteria assessed under the investigations.

The finished product intended for commercialization was manufactured with the same composition (apart from the dosage strengths for lixisenatide and insulin glargine) as the products used throughout clinical development.

Pharmaceutical development

The mono-preparations of respectively, insulin glargine and lixisenatide, are already approved. Therefore the development of the combination product was based on previous experience with the mono-preparations. A pH of 4.5 was demonstrated to be suitable, metacresol is added as preservative, glycerol for tonicity, zinc chloride to stabilise insulin glargine and methionine to stabilise lixisenatide. All excipients are of Ph. Eur. quality and are tested according to their respective monographs.

For the clinical programs, mono-preparations were administered separately, combination products were mixed directly prior to administration and different combination products were administered. Throughout clinical development, the combination product was manufactured with the same composition (apart from the dosage strengths for lixisenatide and insulin glargine) as the finished product intended for commercialization.

Development of Suliqua was based on the marketed formulations for insulin glargine solution for injection 100 U/mL in cartridges and lixisenatide solution for injection 50 or 100 µg/ml.

During development, the critical quality attributes were defined and the physical/chemical stability of the combined product was investigated.

Manufacturing process development has been adequately described, and critical process parameters identified.

The concentration of metacresol was selected and justified by the results of the efficacy of antimicrobial preservation testing.

The container closure system already in use for both mono formulations was selected and the suitability of the cartridges in combination with insulin glargine/lixisenatide solution for injection was successfully demonstrated in extractables and leachables studies.

The description of the pharmaceutical development of the insulin glargine/lixisenatide pen-injector is well documented and raises no cause for concern. The results of the user consultation of the insulin glargine/lixisenatide package leaflets are also provided.

Manufacture of product and process controls

The manufacture, assembly of the disposable pen-injector, testing, primary & secondary packaging, labelling, stability testing, and release has been sufficiently described and validated.

The manufacturing process of the Suliqua finished product includes compounding, pH adjustment, pre-filtration, sterile filtration, filling in cartridges, assembly in the pen-injectors and packaging.

The manufacturing process is considered to be adequately described and relevant in-process controls are performed. The efficacy of aseptic processing, including validation by sterile medial fills, has been demonstrated. The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The specifications for insulin glargine/lixisenatide solution for injection include tests for appearance, identification of actives (HPLC, HPSEC), assay of actives (HPLC), related impurities/degradation products (HPLC), pH (potentiometry), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), particulate matter (Ph. Eur.), antimicrobial preservative assay (HPLC), assay of zinc (AAS), assay of methionine (HPLC) and extractable volume (Ph. Eur.).

The appearance and identification (visual), functional test and dose accuracy of the pen-injector (gravimetry / optical measurement) are also tested.

The specifications for insulin glargine/lixisenatide solution for injection, 100 U/mL insulin glargine with 50 or 33 µg/mL lixisenatide – performed with cartridge are based on batch analyses of several batches of insulin glargine/lixisenatide finished product prepared by the commercial process (three batches of each strength), and five batches used for clinical and toxicological, stability data.

The specifications used for the control of insulin glargine/lixisenatide solution for injection were selected on the basis of the available manufacturing and testing experience, manufacturing process capabilities, regulatory guidance, scientific knowledge, and the stability characteristics.

Appropriate data have been presented to justify the specifications for each quality characteristic that is controlled.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

The validation studies also confirm the suitability of analytical methods for the determination of both sterility and bacterial endotoxins in insulin glargine/lixisenatide solution for injection.

Batch analysis

The provided data are issued from 5 batches used in clinical development (3 x 50 µg and 2 x 22 µg lixisenatide) and 6 representative batches (3 x 50 µg and 3 x 33 µg). All parameters comply with the specification and confirm the consistency of the manufacturing process.

Reference materials

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Stability of the product

The proposed shelf-life of 24 months when the pens are stored in a refrigerator (2°C - 8°C) with an in-use shelf life of 14 days when stored below 30°C, are considered acceptable.

Stability data generated at long-term (5°C±3°C) and accelerated (25°C±2°C/60%±5% RH) storage conditions are provided for 3 batches of each strength of Suliqua in the cartridges and one batch of each strength assembled in the pen injector up to 24 months and 6 months, respectively.

The parameters tested were the same as for release, with the exception of the identification tests. Data from photostability testing (according to ICH Q1B Guideline on Photostability Testing of New Drug Substances and Products) and stress testing (at 40°C±2°C/75%±5% RH for one month) are provided for each of these batches.

In-use stability data are also provided on two batches of each strength of Suliqua tested after storage for 6, 12 and 24 months at long term storage conditions. The data provided are within the proposed specification.

The submitted stability package supports the proposed shelf-life of 24 months when the pens are stored in a refrigerator (2°C - 8°C) with an in-use shelf life of 14 days when stored below 30°C.

Adventitious agents

The risk of potential contamination with adventitious agents in the finished product is deemed very low.

Viral safety

It is considered that no significant risk of contamination with adventitious agents such as mammalian viruses or mycoplasma can be derived from the manufacturing process of starting materials. Therefore, viral clearance studies have not been performed, which is acceptable since no human or animal cell lines are used.

TSE safety

No animal or human derived material is used during the manufacture of the insulin glargine and lixisenatide active substances and the final finished product. Furthermore, it is also declared that both active substances are manufactured in accordance with the note for guidance on minimising the TSE risk (EMEA/410/01).

Taking into account the nature of the product, sufficient information is presented with regard to the risk for potential contamination with adventitious agents in terms of control of materials, control of production process, certification of materials of animal origin and testing of active substance and finished product. These controls make the risk of adventitious agents contamination negligible.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

There were no major objections on quality aspects identified by the CHMP. The CHMP raised a number of other concerns on quality aspects. These were all satisfactorily answered by the applicant during the procedure.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The control applied to the finished product, along with the controls over the manufacturing process of the finished product, support that the product insulin glargine / lixisenatide solution for injection can be routinely manufactured to conform to the current expectations for this type of dosage form. There are no recommendations for future quality development.

Furthermore, the stability data submitted supports that both the active substance and the product will remain of the appropriate quality when stored as recommended storage conditions throughout the proposed re-test period of 48 months for Insulin glargine and 60 months for lixisenatide and a shelf-life of 24 months, for the finished products plus 14 day in-use period.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product 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.

2.2.6. Recommendation(s) for future quality development

n/a

2.3. Non-clinical aspects

The non-clinical package of Suliqua refers to the non-clinical studies conducted with the individual components insulin glargine and lixisenatide that have each undergone complete nonclinical development programs as part of their original marketing authorization application in the EU for the treatment of T2DM under the name Lantus/Optisulin and Lyxumia, respectively.

In support of the application of Suliqua, the following non-clinical studies were further conducted by the Applicant with the insulin glargine/lixisenatide fixed ratio combination:

- A series of in vitro pharmacology studies evaluating the effects of the combination on the binding and activation of the IGF-1R, INSR and GLP-1 R receptors, on cell apoptosis as well as on cell proliferation.
- Primary pharmacodynamics studies assessing the effects of the combination insulin glargine/lixisenatide on glucose homeostasis in a mouse disease model of diabetes as well as following a glucose oral tolerance test in normoglycemic dogs.
- A cardiovascular safety pharmacology study conducted in the anesthetized dog model with insulin glargine/lixisenatide IV co-administration.
- A study on the PK parameter of insulin glargine and lixisenatide in the dog following a single SC administration of the combination.
- Two local tolerance studies with the insulin glargine/lixisenatide combination in New Zealand White Rabbits.

2.3.1. Pharmacology

In vitro studies were mainly performed in 1.1B4 cells, identified to simultaneously express mRNA of GLP-1R, IGF1R and INSR, and the rat thyroid c-cell line RTC6-23, previously shown to co-express functionally active GLP-1R and INSR. No interaction in cellular signalling between lixisenatide and insulin glargine was indicated up to a concentration of 1 nM of the insulin when cAMP formation was measured in RTC 6-23 cells. At 1 µM of insulin glargine (the highest concentration applied), a slight synergism between lixisenatide and insulin glargine became apparent. Lixisenatide did not possess AKT stimulatory activity in RTC6-23 or 1.1B4 cells and did not influence AKT phosphorylation induced by insulin, insulin glargine or the insulin glargine M1-metabolite. Furthermore, Lixisenatide was shown to be a potent ligand of the human GLP-1R with an IC50 value of 1.43 nM while insulin glargine at a concentration of 100 nM didn't show affinity to the GLP-1 receptor. On the other hand, Lixisenatide did not possess binding affinity to IR-B, did not influence the affinity of insulin glargine to IR-B and did not affect IR-auto phosphorylation or the activity of insulin glargine on IR. Lixisenatide neither possessed an activity for IGF1R nor an influence on the activity of insulin glargine on IGF1R. No interaction between lixisenatide and insulin glargine was thus indicated in the in vitro studies performed with the insulin glargine/lixisenatide combination at the level of their specific receptor or receptor downstream signalling.

There was a strong signalling through the GIP receptor by native GIP in the rat (RTC6-23) and human (TT) thyroid C-cell carcinoma cell lines, while signalling through the GLP-1 receptor by the four GLP-1 receptor agonists was only strong in the rat C-cell line and weak in the human C-cell line. These findings are said to further support the conclusion that GLP-1 receptor-mediated C-cell proliferation in rodents after long-term exposure of high concentrations of GLP-1 receptor agonists might be a rodent-specific phenomenon and not relevant for humans.

Lixisenatide did not induce any relevant modulation of the TNF alpha mediated apoptotic signalling pathway in rat RTC 6-23 cells, while a weak anti-apoptotic property of insulin glargine was detected at 1nM and 1µM. The

combination was comparable to the single dose treatment. In the human pancreatic beta cell line 1.1B4, treated with the pro-inflammatory cytokines TNFalpha /IL-ß and INF-gamma, lixisenatide induced a dose dependent reduction of apoptosis both alone (EC50=2.64 pM) and in presence of 1nM (IC50 = 2.89 pM) and 1µM (IC50 = 2.40 pM) insulin glargine, while insulin glargine alone (at 1pM, 1nM or 1µM) was not able to modulate caspase activity. No synergistic and/or additive anti-apoptotic effect for the combination of lixisenatide and insulin glargine was thus detectable in RTC 6-23 cells following treatment with the pro-inflammatory cytokine TNF alpha or in the human pancreatic beta cell line 1.1B4, treated with the pro-inflammatory cytokines TNFalpha /IL-ß and INF-gamma.

The proliferative effect of insulin glargine and lixisenatide and possible interactions of the combination was investigated in the human pancreatic beta cell line 1.1B4. Insulin and insulin glargine induced 14C-thymidine incorporation in a dose-dependent manner with EC50 9.41nM and 0.996 nM, respectively, while lixisenatide alone did not show any effects on 14C-thymidine incorporation (no EC50 values reported). The combination of insulin glargine/lixisenatide displayed comparable incorporation of 14C-thymidine as compared to insulin glargine alone (EC50 0.775 nM as compared to 0.996 nM). No interaction between lixisenatide and insulin glargine was thus either indicated in the in vitro studies on apoptosis or cell proliferation.

In db/db mice the lixisenatide/insulin glargine combination was indicated to be more effective than insulin glargine alone and decreased blood glucose levels to close normal physiological values. In an OGTT (also in db/db mice) treatment with the insulin glargine/lixisenatide combination was significantly more efficacious versus lixisenatide and insulin glargine alone during the absorptive phase and further reduced blood glucose during the postabsorptive phase compared to placebo-treated control mice. When lixisenatide and insulin glargine were given in combination to Beagle dogs the combination was at least similar to the effects of lixisenatide and insulin glargine monotherapy and there was a decrease of blood glucose levels during both the absorptive and postabsorptive phases of the OGTT similar to that of lixisenatide alone during the absorptive phase and to insulin glargine during the postabsorptive phase. Differences between two strengths of insulin glargine in combination was also observed, suggested to reflect an improved long term performance of the 300 U/mL compared to the 100 U/mL formulation. The lixisenatide/insulin glargine combination did not increase insulin glargine's effect on blood glucose during the postabsorptive phase in dogs and the combination thus did not seem to increase the risk for hypoglycaemia.

A cardiovascular safety pharmacology study was conducted in anesthetized dogs with insulin glargine/lixisenatide IV co-administration. Both compounds, when given together, did not modify the effects observed with insulin glargine alone, as there was similar maximal hypoglycemia, similar effect on plasma potassium concomitant with an increased QT interval and changes in T wave morphology. No additional risk was thus identified when both compounds were co-administered, compared to treatment of insulin glargine or lixisenatide individually.

No other Safety Pharmacology studies or studies on Secondary Pharmacodynamics or Pharmacodynamic drug interactions have been performed with the combination. This is considered acceptable.

2.3.2. Pharmacokinetics

Following SC administration of a combination of insulin glargine and lixisenatide to dogs, the exposure (AUC0-8h) to insulin glargine-M1 was not affected by the presence of lixisenatide in the injection solution. Maximum concentration (Cmax) and exposure (AUC0-8h) of lixisenatide were not significantly impacted by insulin glargine. The plasma half-lives of lixisenatide were significantly shorter (1.1 hours; $p<0.05$) after coadministration with insulin glargine as compared with the plasma half-life seen after administration of

lixisenatide alone (1.9 hours). Since the PK of lixisenatide is absorption-controlled, this result is suggestive of a shortened absorption period of lixisenatide in the presence of insulin glargine.

2.3.3. Toxicology

Full nonclinical programs of toxicology studies for the individual compounds were submitted and reviewed as part of the original marketing authorization applications and subsequent supplements for Lantus/Optisulin and Lyxumia, respectively.

Insulin glargine

The toxicology study program of insulin glargine consisted of general toxicity studies (including toxicokinetics and anti-drug antibody analysis) up to 3-, 6- and 12-month duration in mice, dogs and rats, respectively, in vitro and in vivo genotoxicity studies, carcinogenicity studies in mice and rats, reproductive toxicology studies in rats and rabbits, as well as local tolerance studies in rabbits and studies on potential immunogenicity.

In the repeated dose toxicity studies performed by subcutaneous administration of insulin glargine in mice, rats and dogs, the major toxicity findings were related to the pharmacologic action of the drug and included hypoglycemia, hypoglycemic shock and coma with the consequence of death, due to the excessive doses tested in healthy, non-diabetic animals. These clinical findings were associated with histological findings in the pancreas that consisted of a dose-dependent degranulation of the ß cells of the Langerhans islets as well as in some severe cases, in the brain that included cortical infarction and malacic changes in the cortex and in the region of extrapyramidalic nuclei.

Insulin glargine is not genotoxic. The carcinogenic potential was studied in mice and rats. In both species, there was no evidence for treatment related neoplastic findings other than malignant fibrous histiocytomas at the injection site. The increased incidence of this tumour was not attributable to insulin glargine or any excipient, but rather to an effect of the acid pH of the vehicle on local subcutaneous tissues in rodents. This species-specific finding did not represent a cancer hazard for humans.

In reproductive toxicity studies in rats, there were no effects on fertility or embryo-fetal development up to the highest doses tested (10 or 20 U/kg/day, respectively); a reduction of the rearing rate in F1 animals (attributed to hypoglycemia) occurred at 10 U/kg/day. In rabbits, dose dependent hypoglycemia resulted in maternal toxicity (hypoglycemic shock, total litter loss) and embryo-foetal toxicity, including single anomalies, at doses ≥ 1 U/kg/day. Similar effects were obtained with the reference human NPH insulin.

In studies conducted in guinea pigs, rabbits and pigs to evaluate immunogenicity, insulin glargine had a similar or even lower immunogenic potential than human, porcine and bovine insulin.

Local tolerance in a number of rabbit studies was good for single intravenous, paravenous and subcutaneous injections of doses similar to those intended to be used in humans and moderate to good for single intramuscular injection. The formulations used in the repeated dose toxicity studies in mice and rats elicited tissue damage caused by the low pH of these formulations.

Lixisenatide

In rat and mouse exploratory studies single iv or sc doses of lixisenatide (up to 500 µg/kg in mice, up to 5000 µg/kg in rats) resulted only in transient clinical findings such as lethargy, piloerection and decreased activity.

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 effects observed in testes and epididymis could be due to GLP-1R 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.

Reversible adverse microscopic findings in testis and epididymis were also noted in a 8 month study in juvenile dogs that were similar to those seen in the repeat dose toxicity study in adult dogs.

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

Two-year carcinogenicity studies in mice and rats were performed with dose levels up to 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.

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

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. Lyxumia should not be used during pregnancy and it is not recommended in women of child-bearing potential not using contraception.

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.

Specific local tolerance testing in rabbits with the clinical formulation revealed good SC tolerability.

*Insulin glargine/lixisenatide combinatio*n

Both insulin glargine and lixisenatide have thus been extensively studied in toxicology studies and since no additional toxicological effects were expected for the combination product, the applicant considers the toxicology profile of the combination to be adequately tested with both full programs conducted by using the individual compounds. This is agreed with CHMP.

To support the development of the combination product formulation two local tolerability studies in rabbits were conducted with the insulin glargine/lixisenatide combination. Single administration of lixisenatide/insulin glargine to rabbits resulted in a good (SC, IV and IM) to moderate (PV) local tolerability.

Results from toxicological studies included in the original submissions together with the recently performed comparative toxicity study with insulin glargine support the qualification of impurities at the suggested limits.

2.3.4. Ecotoxicity/environmental risk assessment

A claim of exclusion from preparation of an environmental risk assessment is made by the applicant because insulin glargine and lixisenatide are amino acid sequence analogues of naturally occurring peptides. A reference is made to the ERA Guideline where it is stated that "Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment."

It is thus concluded, based on the protein and peptide structure of the compounds that insulin glargine and lixisenatide are not expected to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

A series of in vitro studies was performed to evaluate possible interactions of a combination treatment with insulin glargine and lixisenatide at the cellular level. Effects of the insulin glargine/lixisenatide combination were compared with the effects of both individual components at the level of their specific receptor, on receptor downstream signalling, cell apoptosis and proliferation in vitro. No interaction between lixisenatide and insulin glargine was indicated at the level of their specific receptor or receptor downstream signalling and no interaction regarding effects on apoptosis or cell proliferation was either indicated.

In vivo studies were also performed in order to evaluate if the combination of insulin glargine and lixisenatide shows beneficial metabolic effects over treatment with either drug alone. The effect of the combination was at least similar to the effects of lixisenatide and insulin glargine monotherapy and there was a decrease of blood glucose levels during both the absorptive and postabsorptive phases of the OGTTs performed similar to that of lixisenatide alone during the absorptive phase and to insulin glargine during the postabsorptive phase. No increase of insulin glargine's effect on blood glucose during the postabsorptive phase in dogs was seen and the combination thus did not seem to increase the risk for hypo-glycaemia.

No additional risk for cardiovascular effects was identified when both compounds were co-administered to anesthetised dogs, compared to treatment of insulin glargine or lixisenatide individually.

When pharmacokinetics was analysed in dogs no effect on AUC0-8 of insulin glargine was seen in the presence of lixisenatide in the injection solution and Cmax and AUC0-8h of lixisenatide were neither significantly impacted by insulin glargine. A significant shortening of the plasma half-lives of lixisenatide was seen after coadministration with insulin glargine indicating a shortened absorption period of lixisenatide in the presence of insulin glargine.

To support the development of the combination product formulation two local tolerability studies in rabbits were conducted with the insulin glargine/lixisenatide combination. Single administration of lixisenatide/insulin glargine to rabbits resulted in a good (SC, IV and IM) to moderate (PV) local tolerability. Both insulin glargine and lixisenatide have been extensively studied in toxicology studies and no additional toxicological effects are expected for the combination product, the toxicology profile of the combination is considered to have been adequately tested with both full programs conducted by using the individual compounds.

Results from toxicological studies included in the original submissions together with the recently performed comparative toxicity study with insulin glargine support the qualification of impurities at the suggested limits.

The active substances are analogues of naturally occurring peptides and are not expected to pose a risk to the environment.

2.3.6. Conclusion on non-clinical aspects

The data provided in the non-clinical part of the dossier was considered to be satisfactory in the view of the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

- **Tabular overview of clinical studies**

Table 1: overview of phase 1 studies

Study	Study type	Population (Number of subjects[a])	Ratios of insulin glargine/lixisenatide
Definitive studies (in support of fixed ratio of insulin glargine and lixisenatide)			
BDR10880	PK + PD	T1DM (42)	1.5, 4.0 U/1 µg
BDR12547	PK	Healthy (16)	0.5, 1.0, 2.0 U/1 µg
Preliminary studies (in support of titrated insulin glargine/ fixed lixisenatide dose)			
BDR11578	PK + PD	T1DM (23)	1.7 – 2.8 U/1 µg
BDR11540	PK	Healthy (24)	0.25, 0.5 U/1 µg
Exploratory studies (concentrations of insulin glargine not intended for marketing)			
BDR11038	PK + PD	T1DM (26)	0.25, 1.3 – 1.9 U/1 µg
PKD12406	PK	Healthy (20)	1.0, 2.0, 4.0 U/1 µg

a Number of subjects randomized and treated

PD = pharmacodynamic(s); PK = pharmacokinetic(s); T1DM = type 1 diabetes mellitus

A phase 2 proof-of concept study (ACT12374) was performed. This was a 24-week, open-label, 2-arm, parallel-group, multicenter study comparing the efficacy and safety of the FRC versus insulin glargine in combination with metformin in which 323 patients were randomized.

Table 2 Completed Phase 3 trials for the demonstration of efficacy and safety of the fixed-ratio combination (lixisenatide and insulin glargine)

Trial description	Treatment and dosing	Population	Antidiabetic treatment at Screening	No. of subjects randomized	Endpoints
EFC12404 Three-arm (fixed-ratio combination, glargine, lixisenatide), all with metformin Randomized, open-label Duration of 30 weeks 4-week run-in period to optimize metformin and stop 2nd OAD (if taken)	**Fixed-ratio combination (FRC) and insulin glargine groups:** Daily dose during the first week of treatment was 10 U. After the first week, doses were adjusted once weekly to achieve target fasting SMPG of 4.4 to 5.6 mmol/L (80 to 100 mg/dL) while avoiding hypoglycemia. The maximum daily dose of the FRC and of glargine was capped at 60 U (in the FRC corresponding to a lixisenatide dose of 20 µg) **Fixed ratio combination** could be titrated from 10 to 60 U glargine/5 to 20 µg lixisenatide. The lixisenatide dose increased or decreased along with the glargine dose. Only the dose of glargine appeared in the pen dosing window. Two pens were available: • Pen A (administration of daily combination doses between 10 U/5 µg and 40 U/20 µg) was used for starting combination treatment • Pen B for daily combination doses between 30 U/10 µg and 60 U/20 µg) was used when a higher dose of the combination was required. Lixisenatide was initiated at 10 µg QD for 2 weeks; a maintenance dose of 20 µg QD was to be used for the duration of treatment, tolerability allowing.	Patients with T2DM insufficiently controlled on metformin ± a second OAD. HbA1c at Screening >7.5% and <10% (patients on metformin alone) HbA1c at Screening >7.0% and <9.0% (patients on metformin plus a second OAD) At the end of the 4-week run-in period: • HbA1c ≥7.0% and ≤10.0% • FPG ≤13.9 mmol/L (≤250 mg/dL)	Metformin ± a second OAD (sulfonylurea [SU], a glinide, a sodium-glucose co-transporter-2 inhibitor, or a dipeptidyl peptidase-4 inhibitor) OADs other than metformin were discontinued. Daily metformin dose was increased weekly during the run-in phase to a final daily dose of at least 2000 mg or up to the maximal tolerated dose which had to be ≥1500 mg/day to allow randomization Only metformin was continued at a MTD of ≥1500 mg/day, to be maintained at a stable dose throughout the study unless safety issues arose.	Randomized 2:2:1 (fixed-ratio combination: insulin glargine: lixisenatide) FRC: N=469 Insulin glargine: N=467 Lixisenatide: N=234	**Co-primary**: Superiority of fixed-ratio combination versus lixisenatide and non-inferiority versus insulin glargine in change in HbA1c from baseline to Week 30 If non-inferiority versus insulin glargine was demonstrated, superiority was also tested as specified in the hierarchical testing order. **Safety**: To assess safety and tolerability in each treatment group
EFC12405 Two-arm (fixed-ratio combination, insulin glargine) with or without metformin Randomized, open-label Duration of 30 weeks 6-week run-in period to optimize/switch to insulin glargine and stop any OAD other than metformin	**Two arms:** - FRC - Insulin glargine (100 U/mL) alone **6-week run-in phase:** Switch to insulin glargine (if other basal insulin taken) and dose titration. Discontinuation of OAD other than metformin. **Randomized treatment period:** Starting dose: **FRC**: 20 U/10 µg (Pen A) if glargine dose on the day before randomization was <30 U; 30 U/10 µg (Pen B) if glargine dose on the day before randomization was ≥30 U. The dose was to remain stable for 2 weeks. **Insulin glargine**: same dose as the one received on the day before randomization Titration FRC and glargine doses adjusted once weekly to achieve target fasting SMPG of 4.4 to 5.6 mmol/L (80 to 100 mg/dL) while avoiding hypoglycemia. Maximum FRC dose: 60 U/20 µg; Maximum glargine dose: 60 U	Patients with T2DM insufficiently controlled on a stable basal insulin regimen with a daily dose (± 20%) between 15 and 40 U/day **At screening:** FPG ≤10.0 mmol/L (≤180 mg/dL) for patients receiving basal insulin in combination with 2 OADs or with 1 OAD other than metformin FPG ≤11.1 mmol/L (≤200 mg/dL) for patients on basal insulin only or basal insulin plus metformin **At the end of the 6-week run-in period:** • HbA1c ≥7.0% or ≤10.0% • Mean fasting SMPG ≤7.8 mmol/L (≤140 mg/dL), calculated for the 7 days before randomization • Average insulin glargine daily dose ≥20 U or ≤50 U calculated for the last 3 days before randomization	Metformin ± OAD(s) OADs could be 1 to 2 out of a SU, a glinide, a SGLT2-inhibitor, or a DPP-4 inhibitor. Only metformin could be continued during the study, at ≥1500 mg/day or MTD, to be maintained at a stable dose throughout the study unless safety issues developed.	Randomized 1:1 FRC: N=367 Insulin glargine: N=369	**Primary**: Superiority of the fixed-ratio combination versus insulin glargine in change in HbA1c from baseline to Week 30 **Safety:** To assess safety and tolerability in each treatment group.

FRC, fixed-ratio combination; FPG, fasting plasma glucose; MTD, maximum tolerated dose; OAD, oral antidiabetic drug; PG, plasma glucose; PPG, postprandial plasma glucose; QD, once daily; SMPG, self-monitored plasma glucose; SU, sulfonylurea

2.4.2. Pharmacokinetics

Suliqua is applied as two prefilled pens with different fixed ratios between insulin glargine and lixisenatide, the 10-40 U pen with a ratio of 2U insulin glargine/1 µg lixisenatide and the 30-60 Unit pen with a ratio of 3U insulin glargine/1 µg lixisenatide. In both pens the concentration of insulin glargine is 100 U/ml and the concentration of lixisenatide is 50 µg/ml and 33 µg/ml respectively.

The clinical pharmacology file of the fixed ratio combination is referring to data from the mono-components. Six phase 1 studies are submitted in support of the clinical pharmacology properties of the combination. Two different formulation approaches were investigated during the development: combinations of a fixed ratio of insulin glargine and lixisenatide (supported by studies BDR10880 and BDR12547) and combinations of individually titrated doses of insulin glargine with a fixed-dose of lixisenatide (supported by studies BDR11578 and BDR11540). In each of these studies the concentration of insulin glargine used was 100 U/ml, which is the same as in Lantus and in the combination product intended for marketing. Based on technical feasibility, the fixed-ratio approach was selected for further clinical development while combinations of a fixed dose of lixisenatide with individually titrated doses of insulin glargine were not further pursued. In 2 exploratory studies (BDR11038 and PKD12406), insulin glargine concentrations other than 100 U/mL intended for marketing were administered (approximately 60, 90, and 300 U/mL) in combination with lixisenatide. These concentrations were not further pursued.

The formulation of the fixed ratio combination used in the phase 3 studies is identical to the proposed commercial formulation. The composition of the two dosage strengths intended for marketing are also comparable to the composition of the marketed mono-components insulin glargine (Lantus) and lixisenatide (Lyxumia).

Total lixisenatide was determined with a validated enzyme-linked immunosorbent assay (ELISA) using a double-antibody technique. Free insulin glargine was measured with a validated radioimmunoassay (RIA) method using a human insulin RIA kit.

Anti-lixisenatide antibodies were assessed by Surface Plasmon Resonance (SPR) method and anti-insulin antibodies were assessed using radioimmunoprecipitation (RIP) methods.

Pharmacokinetic parameters were calculated by non-compartmental methods.

Absorption

Data from the individual files describe a rapid absorption of lixisenatide that is not influenced by the administered dose following subcutaneous administration to patients with type 2 diabetes (median t_{max} of 1 to 3.5 hours). The extent of absorption was independent of injection site, while the rate of absorption was somewhat slower after administration in the thigh than in the arm or abdomen. These differences in rate of absorption were however not considered clinically relevant.

For insulin glargine, insulin serum concentrations indicated a slower and much more prolonged absorption and showed a lack of a peak after subcutaneous injection of insulin glargine in comparison to human NPH insulin (intermediate-acting human insulin).

Bioavailability

Study BDR10880 was a randomised, cross-over, single-dose, open, euglucaemic clamp study on the relative bioavailability and activity of two different fixed ratio formulations of insulin glargine and lixisenatide compared to separate simultaneous injections performed in 42 subjects with T1DM. Blood samples were collected pre-dose and up to 24 hours post-dose. The test formulations were premixed formulations of lixisenatide 66 µg/ml and insulin glargine 100 U/ml (1.5 U/1µg) given at a dose of 0.264 µg/kg and 0.4 U/kg (test 1) and lixisenatide 25 µg/ml and insulin glargine 100 U/ml (4 U/1µg) given at a dose of 0.100 µg/kg and 0.4 U/kg (test 2). Reference formulations were separate simultaneous injections of lixisenatide 100 µg/ml and insulin glargine 100 U/ml given at corresponding doses.

Table 3: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for lixisenatide

Treatment	AUC_{0-t} pg*h/ml	AUC_{inf} pg*h/ml	C_{max} pg/ml	t_{max} h
Test 1 (n=20)**	559±262	664±243	96.8±44.2	3.00 (2.00-5.00)
Reference 1 (n=21)	627±236	694±242	137±42.4	2.00 (1.00-4.00)
*Ratio (90% CI) (T1/R1)	0.82 (0.68-0.99)	0.92 (0.78-1.08)	0.66 (0.57-0.77)	-
Test 2 (n=20)	213±78.6	273±73.0	47.3±11.5	2.50 (1.00-3.00)
Reference 2 (n=20)	222±65.2	280±68.3	60.8±14.0	1.75 (0.50-3.00)
*Ratio (90% CI) (T2/R2)	0.93 0.77-1.11	0.97 (0.83-1.13)	0.78 (0.68-0.88)	-

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*
***Subject 02 excluded due to flawed injection (iv profile)*

Table 4: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax and t50%-AUC0-24h median, range) for insulin glargine

Treatment	AUC_{0-24h} µU*h/ml	C_{max} µU /ml	t_{max} h	$t_{50\%}$-AUC_{0-24h} (h)
Test 1 (n=20)	221±87.3	13.8±6.99	10.00 (0.25-16.00)	11.340 (9.36-12.94)
Reference 1 (n=19)	255±85.4	14.9±5.05	12.00 (2.00-16.00)	11.750 (8.56-12.64)
*Ratio (90% CI)	0.86 (0.77-0.96)	-	-	-
Test 2 (n=18)	221±68.3	12.4±4.40	10.00 (0.25-14.00)	11.610 (9.85-13.47)
Reference 2 (n=21)	267±96.0	15.7±9.32	12.00 (2.00-16.00)	11.760 (8.48-12.99)
*Ratio (90% CI)	0.88 (0.79-0.98)	-	-	-

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Study BDR12547 was a randomised, 4-treatment, 4-period, 4-sequence cross-over study comparing the relative bioavailability of lixisenatide from three different premixed formulations of lixisenatide/insulin glargine in healthy subjects. The tested formulations contained 100 IU/ml insulin glargine and 50 µg/ml (F1; ratio 2 IU/1 µg), 100 µg/ml (F2; ratio 1 IU/1 µg) or 200 µg/ml (F3; ratio 0.5 U/1 µg) lixisenatide respectively. Each formulation was given at a lixisenatide dose of 20 µg as follows:

Treatment A: 20 µg lixisenatide and 10 U insulin glargine (1 injection of 100 µl of F3)

Treatment B: 20 µg lixisenatide and 20 U insulin glargine (1 injection of 200 µl of F2)

Treatment C: 20 µg lixisenatide and 40 U insulin glargine (1 injection of 400 µl of F1)

Treatment D: 20 µg lixisenatide and 40 IU insulin glargine (4 separate sequential injections of 100 µl of F1).

Blood samples were collected pre-dose and up to 36 hours post-dose.

For AUC_{inf} and AUC_t the 90% confidence interval for the treatment ratios fell within the conventional acceptance range of 80.00-125.00% and for C_{max} all point estimates and CIs were within the bioequivalence interval except for the lower limits for treatment ratios A/C and A/D which were just below the bioequivalence limit.

Study BDR11578 was a randomised, single-dose, two-treatment, two-sequence, cross-over, euglycaemic clamp study on the relative bioavailability and activity of 0.6 U/kg insulin glargine (100 U/ml) and 20 µg lixisenatide, given as an on-site mix administered as a single injection at 1 periumbilical site compared to separate simultaneous injections at opposite periumbilical sites in 23 patients with T1DM. Blood samples were collected pre-dose and up to 24 hours post-dose.

Table 5: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for lixisenatide.

Treatment	AUC_{0-t} pg*h/ml	$AUC_{0-\infty}$ pg*h/ml	C_{max} pg/ml	t_{max} h
Test (on-site mix) (n=21)	**497±126**	**581±134**	**100±27.0**	**2.50 (1.50-5.00)**
Reference (separate) (n=22)	**531±117**	**601±134**	**116±24.7**	**2.00 (1.00-3.00)**
***Ratio (90% CI)**	**0.92 (0.80-1.06)**	**0.96 (0.83-1.10)**	**0.84 (0.74-0.96)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 6: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for insulin glargine

Treatment	AUC_{0-24h} µU*h/ml	C_{max} µU /ml	t_{max} h
Test (on-site mix) (n=21)	**302±122**	**17.2±6.72**	**10.00 (2.00-18.00)**
Reference (separate) (n=22)	**291±99.4**	**16.6±6.44**	**11.00 (8.00-14.00)**
***Ratio (90% CI)**	**1.01 (0.90-1.14)**	**-**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Study BDR11540 was a randomised, single-dose, three-treatment, six-sequence, three-period cross-over study comparing the bioavailability of 20 µg lixisenatide from two on-site mixtures in two strengths (400 µg/ml and 200 µg/ml) in Lantus to lixisenatide (100 µg/ml) alone in 24 healthy male and female subjects. Blood samples were collected pre-dose and up to 12 hours post-dose.

• T1 = 50 µL on-site mix of lixisenatide in Lantus 100 U/ml (400 µg/mL), yielding 20 µg lixisenatide with 5 U Lantus 100 U/ml (ratio 0.25 U/1 µg)

• T2 = 100 µL on-site mix of lixisenatide in Lantus 100 U/ml (200 µg/mL), yielding 20 µg lixisenatide with 10 U Lantus 100 U/ml (ratio 0.5 U/1µg)

• R = 200 µL lixisenatide (100 µg/mL), yielding 20 µg lixisenatide

Table 7: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for lixisenatide, n=24

Treatment	AUC_{0-t} pg*h/ml	$AUC_{0-\infty}$ pg*h/ml	C_{max} pg/ml	t_{max} h
Test 1	343±115	394±128	65.6±17.0	2.50 (1.00-5.00)
Test 2	328±111	391±123	68.4±17.3	2.50 (1.00-8.00)
Reference	555±177	621±200	128±38.4	1.50 (0.50-3.08)
*Ratio (90% CI) (T1/R)	0.62 (0.54-0.70)	0.64 (0.56-0.73)	0.52 (0.47-0.57)	-
*Ratio (90% CI) (T2/R)	0.60 (0.53-0.68)	0.65 (0.56-0.75)	0.54 (0.50-0.58)	-
*Ratio (90% CI) (T1/T2)	1.04 (0.95-1.13)	0.99 (0.89-1.10)	0.95 (0.89-1.02)	-

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Study PKD12406 was a randomized, 4-treatment, crossover study on the relative bioavailability of lixisenatide in insulin glargine solution in 20 healthy subjects. Three different test formulations were tested with different concentrations of lixisenatide (75, 150 and 300 µg/ml) and with the same concentration of insulin glargine (300 U/ml). The reference was lixisenatide monotherapy in the same dose (15 µg). For the comparisons of the 3 combination treatments (Treatments B, C, and D) to Treatment A (lixisenatide without insulin glargine), lixisenatide exposure was generally comparable between the treatments, with point estimates of exposure (based on $AUC_{0-\infty}$, AUC_{0-t}, and AUC_{0-12}) between 0.83 and 0.96, but not all CIs were entirely within the standard equivalence boundary of 0.8 to 1.25. The maximum concentration of lixisenatide when coadministered with insulin glargine was reduced compared to the injection of lixisenatide alone, with point estimates of the ratios ranging from 0.64 to 0.76.

Bioequivalence

Since the final formulation was used in the phase 3 studies, no bioequivalence study between clinical formulation and commercial formulation was necessary.

Influence on absorption of site of injection or fat layer thickness

According to data from the mono-components there were no clinically relevant differences in serum insulin levels after abdominal, deltoid or thigh administration of insulin glargine. For lixisenatide monotherapy, 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 C_{max} (mean ratio 0.86). These differences in rate of absorption were however not considered clinically relevant. Both mono-components can be given in the thigh, abdomen or upper arm/deltoid.

The applicant argues that following administration of the insulin glargine/lixisenatide fixed ratio combination, effects on the PK of the individual components are mainly caused by interactions occurring in the SC tissue at the injection site. These interactions are expected to be independent of the injection site itself. Therefore, no specific study was conducted to investigate the effect of different injection sites on the PK of insulin glargine and lixisenatide following administration of the combination product. In the Phase 3 studies, patients could select between thigh, abdomen or upper arm for injection of the insulin glargine/lixisenatide fixed ratio combination.

Influence on absorption of fat layer thickness has not been addressed by the applicant.

Distribution

According to data from the mono-component, 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.

For the combination, the following data regarding lixisenatide is available. In study BDR10880 in T1DM patients Vz/F of lixisenatide was 126 and 91.1 L at insulin glargine/lixisenatide ratios of 1.5U/1 µg and 4U/1 µg respectively. Also in healthy volunteers (study BDR12547) Vz/F for lixisenatide was around 100 l at insulin glargine/lixisenatide ratios of 0.5, 1 and 2 U/1µg.

For insulin glargine, Vss/F was 1760 and 1660 L at insulin glargine/lixisenatide ratios of 1.5U/1µg and 4U/1µg according to results from study BDR10880.

Elimination

After subcutaneous injection of Lantus in diabetic patients, insulin glargine is rapidly metabolized at the carboxyl terminus of the Beta chain with formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). In plasma, the principal circulating compound is the metabolite M1. The exposure to M1 increases with the administered dose of Lantus. The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with Lantus is principally based on exposure to M1. Further degradation is assumed to be similar to endogenous insulin. Since no influence of lixisenatide on the metabolism of insulin glargine was expected, no metabolism studies were performed with the combination.

As a peptide, lixisenatide is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation, resulting in smaller peptides and amino acids, which are reintroduced in the protein metabolism. The underlying metabolic processes are considered to be generally understood and no metabolite profiling has been performed. Therefore, no metabolism studies were performed with the combination. After multiple dose administration in patients with type 2 diabetes, mean terminal half-life was approximately 3 hours and the mean apparent clearance (CL/F) about 35 L/h.

Dose proportionality and time dependency

In study BDR10880 with T1DM patients, in which approximately 8 and 21 µg lixisenatide were administered with insulin glargine at doses of approximately 30 U in the combination, the statistical analysis of dose proportionality for this 2.6-fold increase in lixisenatide dose indicated that the AUC increased in a dose proportional manner. C_{max} increased less-than proportional with dose.

In Studies BDR10880 and BDR11578, the AUC of insulin glargine administered as insulin glargine/lixisenatide combination or separate simultaneous injections increased with increasing dose of insulin glargine. In study BDR10880 an AUC_{0-24h} of 221 µU*h/ml was achieved with a 0.4 U/kg dose of insulin glargine, while in study BDR11578 an AUC_{0-24h} of 302 µU*h/ml was achieved with a 0.6 U/kg dose of insulin glargine (in both cases with the insulin glargine/lixisenatide combination).

According to previous results from the mono-component lixisenatide seems to display time independent pharmacokinetics and has no accumulation in subjects with no anti-lixisenatide antibodies. Following administration of the combination, the lixisenatide PK profile reaches C_{max} after approximately 2.0 to 3.0 hours and returns back to values below the limit of quantification well before 24 hours in anti-lixisenatide antibody negative subjects. Thus, no relevant accumulation of lixisenatide is to be expected following repeated administration of the combination and was therefore not investigated.

Following repeated administration of insulin glargine alone, no accumulation was observed. Lixisenatide has shown to have no relevant impact on the PK of insulin glargine when administered as combination. Therefore, accumulation of insulin glargine when administered as combination was not investigated.

Intra- and inter-individual variability

The inter-individual variability for AUC and C_{max} of lixisenatide and insulin glargine when given as a fixed ratio combination was generally moderate. In study BDR10880 CV was 25-50 % for lixisenatide and 30-50% for insulin glargine and in study BDR12547 CV was 30-40% for lixisenatide.

For lixisenatide monotherapy the inter-individual variability for the PK parameters was generally moderate (CV was for the most part approximately 30% to 60%). In the bioequivalence study which had a replicate design, the within-subject variation was estimated to be 27% for $AUC_{0-\infty}$ and 22% for C_{max}. In the population analysis the estimated inter-occasion variability in absorption was around 35%.

For insulin glargine monotherapy the intra-subject CV in study 1012 was 14% for $AUC_{0-24\ h}$ and 28 % for C_{max} while the inter-subject CV was 25% for $AUC_{0-24\ h}$ and 36% for C_{max}.

Pharmacokinetics in target population

The phase 1 studies with the combination were performed in healthy volunteers or in patients with type 1 diabetes mellitus. Sparse sampling was performed in the phase 2 and in the phase 3 studies in patients with type 2 diabetes mellitus with assessment of lixisenatide.

Between-study comparison from lixisenatide monotherapy suggests similar lixisenatide exposure in T2DM patients and healthy volunteers. Using mixed effects modelling, a population PK model was developed for lixisenatide monotherapy. Given the minor differences in the PK profile of lixisenatide when given in combination compared to when given in separate simultaneous injections and the high inter-occasion variability, the impact of the combination on the existing population PK model for lixisenatide was not evaluated.

Insulin absorption was similar in type 2 diabetic subjects as compared to healthy volunteers according to data from insulin glargine monotherapy. Doses of insulin glargine when administered alone or in combination with

lixisenatide are determined individually according to patient's FPG values. Therefore, no population PK model was established for insulin glargine.

Special populations

The impact of insulin glargine on the PK of lixisenatide is regarded to be confined solely due to an effect on the absorption from the subcutaneous depot. Therefore, the impact of intrinsic (primarily body weight, renal function and anti-drug antibodies) and extrinsic factors on the PK of lixisenatide is not altered once the peptide has reached the blood circulation. Based on this rationale no specific PK studies were conducted to evaluate potential intrinsic sources of PK variability of insulin glargine or lixisenatide following administration of the insulin glargine/lixisenatide combination. However, in Study ACT12374 in patients with T2DM, information on the influence of anti-lixisenatide antibodies on the plasma concentrations of lixisenatide in patients treated with the insulin glargine/lixisenatide combination is generated. Data in special populations with the monotherapies is summarised below.

Impaired renal function

In subjects with mild (creatinine clearance calculated by the Cockcroft-Gault formula 60-90 ml/min), moderate (creatinine clearance 30-60 ml/min) and severe renal impairment (creatinine clearance 15-30 ml/min) AUC of lixisenatide was increased by 46%, 51% and 87%, respectively.

The pharmacokinetics of insulin glargine were not evaluated in special populations (e.g. patients with impaired renal or liver function), nor was the influence of gender, age or race. It is expected that modifications to pharmacokinetics and pharmacodynamics occurring with insulin glargine in subjects with impaired renal and hepatic function will be similar to modifications observed with human insulin. A warning for diminished insulin requirements in renal and hepatic impairment, and a steady decrease in insulin requirements in the elderly has been included in the SmPC. In the light of these warnings and since the dose must be individually adjusted to each patient, the lack of pharmacokinetic data in sub-populations was considered acceptable for insulin glargine.

Impaired hepatic function

As lixisenatide is cleared primarily by the kidney, no pharmacokinetic study has been performed in patients with acute or chronic hepatic impairment. Hepatic dysfunction is not expected to affect the pharmacokinetics of lixisenatide.

Gender

Gender has no clinically relevant effect on the pharmacokinetics of lixisenatide.

The influence of gender on the pharmacokinetics of insulin glargine was not evaluated. In clinical studies, subgroup analyses based on gender did not indicate any difference in safety and efficacy in insulin glargine-treated patients compared to the entire study population.

Race

Ethnic origin had no clinically relevant effect on the pharmacokinetics of lixisenatide based on the results of pharmacokinetic studies in Caucasian, Japanese and Chinese subjects.

Weight

Body weight has no clinically relevant effect on lixisenatide AUC.

Elderly

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.

The influence of age on the pharmacokinetics of insulin glargine was not evaluated. In clinical studies, subgroup analyses based on age did not indicate any difference in safety and efficacy in insulin glargine-treated patients compared to the entire study population.

Children

No studies have been performed with the combination product in patients below 18 years of age. A product specific waiver (EMEA-000915-PIP01-10) from investigating the effects of this FRC for the treatment of T2DM in the paediatric population has been accepted.

Subjects with anti-insulin glargine antibodies

Anti-insulin antibodies were determined in all Phase 2 and 3 multiple-dose studies with the combination. The effect of anti-insulin antibodies on insulin exposure was not investigated in the combination studies.

Subjects with anti-lixisenatide antibodies

From studies with lixisenatide monotherapy it is known that lixisenatide PK is greatly influenced by presence of lixisenatide antibodies. For example in Study DRI6012, in which patients were treated in parallel groups at doses of 5 to 30 µg QD or BID for 13 weeks, the mean $AUC_{[04.5h]}$ and C_{max} values for total lixisenatide in antibody-positive patients were up to 13.7-fold higher than in antibody-negative patients. The pharmacokinetics was therefore mainly evaluated in subjects and patients without anti-lixisenatide antibodies.

Anti-lixisenatide antibodies were determined in all Phase 1 single-dose studies with the combination as well as in all Phase 2 and 3 multiple-dose studies. Three subjects in the single-dose studies in healthy subjects (2 in BDR12547 and 1 in PKD12406) and 6 patients in the single-dose study BDR10880 in patients with T1DM were recorded as having anti-lixisenatide antibodies. Three of the 6 anti-lixisenatide antibody positive patients in Study BDR10880 were antibody positive at baseline. In 8 of 9 of the cases, the PK profiles of lixisenatide in antibody-positive individuals were within the ranges found for antibody-negative individuals.

In the multiple-dose Phase 2 Study ACT12374, following treatment of patients with T2DM with the insulin glargine/lixisenatide combination for 24 weeks, 72 out of 147 patients (49.0%) had anti-lixisenatide antibodies. In line with observations in the lixisenatide monotherapy studies, the presence of anti-lixisenatide antibodies resulted in up to approximately 10-fold increases in plasma concentrations of total lixisenatide.

Interactions

As peptides, insulin glargine and lixisenatide are subject to standard proteolytic processes involving degradation to small peptides and amino acids; both peptides are not expected to be metabolized by CYP isozymes. Insulin glargine is expected to be eliminated like human insulin. Lixisenatide is assumed to be eliminated through renal filtration followed by tubular reabsorption and subsequent metabolic degradation. Due to the nature of the proteolytic processes and the different pathways of degradation, no interaction between circulating insulin glargine and lixisenatide is expected. The impact of insulin glargine on the PK of lixisenatide is regarded to be confined solely due to an effect on the absorption from the subcutaneous depot. Coadministered drugs that

inhibit or induce metabolic pathways are expected to have no effect on the systemic exposure to insulin glargine and lixisenatide.

In vitro

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.

No data are available for insulin glargine.

In vivo

There are no known pharmacokinetic interactions for insulin glargine.

In vivo lixisenatide delays gastric emptying and may thereby reduce the extent and rate of absorption of orally administered drugs. The influence of lixisenatide monotherapy 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 t_{max} and a reduction in C_{max}, which was dependent on when lixisenatide was administered in relation to the concomitantly administered drug. 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. The SmPC also states that patients receiving medicinal products of either a narrow therapeutic ratio or medicinal products that require careful clinical monitoring should be followed closely, especially at the time of initiation of lixisenatide treatment and that these medicinal products should be taken in a standardised way in relation to lixisenatide.

For the combination product, a decrease in C_{max} by approximately 30% and a delay in t_{max} of lixisenatide by 1 hour at unchanged exposure have been observed compared to separate simultaneous injections of lixisenatide and insulin glargine (study BDR10880). The applicant has performed simulations applying the population PK/PD model describing the correlation between lixisenatide concentration and inhibition of gastric emptying, demonstrating that recovery of gastric empyting to baseline occurs within 11 hours after administration of the maximum intended dose of lixisenatide of 20 µg in the fixed ratio combination as well as with 20 µg of lixisenatide given alone.

2.4.3. Pharmacodynamics

Mechanism of action

Insulin glargine

The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

Lixisenatide

Lixisenatide is a DPP-4 resistant glucagon-like peptide (GLP1) receptor agonist. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from

beta cells and suppresses glucagon from alpha cells in the pancreas. Similar to endogenous GLP-1, the action of lixisenatide is mediated via a specific interaction with GLP-1 receptors, including those on pancreatic alpha and beta cells.

Lixisenatide stimulates glucose dependent insulin secretion. In parallel, glucagon secretion is suppressed. Lixisenatide also slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in blood circulation. Lixisenatide has been shown to preserve beta cell function and to prevent cell death (apoptosis) in isolated human pancreatic islet cells.

Insulin glargine/lixisenatide combination

The postprandial plasma glucose (PPG) lowering effect of lixisenatide, mediated in part by a sustained ability to delay gastric emptying, is associated with a reduction of HbA1c, a limited risk for hypoglycaemia and a weight-lowering effect. With regard to the combination therapy with basal insulin these effects of lixisenatide are complementary to the glucose-lowering effect of basal insulin, which primarily targets fasting plasma glucose (FPG) and on its own can increase the risk for hypoglycemia and weight gain.

Primary pharmacology

Study BDR10880 investigated the pharmacodynamics of insulin glargine and lixisenatide as a fixed ratio combination compared to the pharmacodynamics of each substance administered as separate simultaneous injections under euglycaemic clamp conditions in patients with T1DM. Following administration of the insulin glargine/lixisenatide combination at 2 different strengths (0.4 U/kg insulin glargine + 0.264 µg/kg lixisenatide, and 0.4 U/kg insulin glargine + 0.100 µg/kg lixisenatide), the PD activity, as assessed by the results of GIR-AUC_{0-24h}, were comparable to the corresponding separate simultaneous injections of insulin glargine and lixisenatide with treatment/reference ratios of 0.95 (90% CI: 0.76 to 1.18) and 0.83 (90% CI: 0.61 to 1.12), respectively.

Thus adding lixisenatide to insulin glargine solution had little to no impact on the PD of insulin glargine; GIR-AUC_{0-24h} and GIR_{max} being comparable for the combination and separate simultaneous injections. The impact of the combination of insulin glargine and lixisenatide on the pharmacodynamics of lixisenatide has not been studied in Phase 1 studies.

Consistent with a relatively constant concentration/time profile of insulin glargine over 24 hours with no pronounced peak when administered alone, the glucose utilization rate/time profile was similar, no pronounced peak, when given in the combination insulin glargine/lixisenatide.

Study BDR11578 is considered supportive for BDR10880. This was a euglycaemic clamp study conducted in patients with T1DM. This study also demonstrated that adding lixisenatide to insulin glargine solution had little to no impact on the PD of insulin glargine; GIR-AUC_{0-24h} and GIR_{max} being comparable for the combination and separate simultaneous injections.

Insulin glargine studies

Clinical pharmacology studies have demonstrated that insulin glargine administered once-daily is effective in maintaining glycaemic control as assessed by reductions in HbA1c in subjects with T1DM or T2DM. The glucodynamic effects of insulin glargine are the result of its delayed and predictable absorption from the subcutaneous injection site resulting in a smooth time-action profile with no pronounced peak

Lixisenatide studies

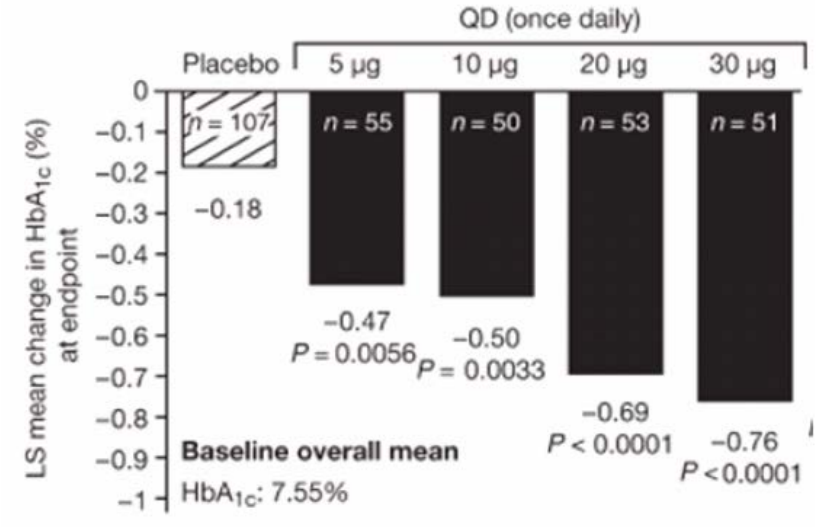
Data from lixisenatide monotherapy studies PDY12545, ACT6011 and DRI6012 provide supplementary information on the mode of action as well as the pharmacodynamic effects of lixisenatide at doses below 20 µg.

The clinical pharmacology findings from studies with lixisenatide have demonstrated PD effects consistent with potent GLP-1 receptor agonism, including a pronounced reduction in PPG levels, a sustained delay in gastric emptying, as well as glucagonostatic properties in patients with T2DM (ACT6011 and DRI6012). Lixisenatide induced reductions in PPG concentrations after breakfast, lunch, and dinner, when compared with placebo, most notably with the first meal after administration. This effect was maintained after 28 days of once-daily treatment. Assessed for the first meal after lixisenatide administration, the PPG effects were accompanied by gastric emptying and reduced insulin secretion. Because delay of gastric emptying prolongs absorption of meal-derived glucose and has the capacity to blunt PPG excursions, the pronounced decrease in PPG with lixisenatide can be related to the significant and sustained delay in gastric emptying. Additional PD effects are stimulation of insulin release in response to an intravenous glucose challenge, with restoration of first- and second-phase insulin secretion. Fasting blood glucose concentrations in patients with T2DM were also reduced during multiple-dose treatment with lixisenatide as compared with placebo. As expected for a GLP-1 receptor agonist, counter-regulatory glucagon responses to hypoglycaemia are not impaired by lixisenatide in subjects with insulin-treated T2DM.

Additional studies have shown that 5, 10, and 20 µg lixisenatide once-daily provided a significant reduction in PPG levels in patients with T2DM (ACT6011). A significant delay of gastric emptying (measured by acetaminophen absorption) with concomitant reductions in PPG were seen in healthy subjects with doses of 5, 10, and 20 µg compared to placebo (PDY12545).

In accordance with the label, lixisenatide is initiated with QD injections of 10 µg for 2 weeks. The lixisenatide dose is then increased to a maintenance dose of 20 µg QD. The lower end of the lixisenatide dosing range is defined by the minimum dose for glycaemic efficacy in the placebo-controlled dose-ranging study DRI6012, where doses beginning at 5 µg once-daily provided HbA1c and PPG control. Data from this study indicated that the PPG-lowering effect translates to a significant reduction in HbA1c following 13 weeks of treatment, including the dose levels of 5 and 10 µg lixisenatide (Figure 1).

Figure 1 Study DRI6012: Changes in HbA1c levels following 13 weeks treatment with lixisenatide QD, according to dose and regimen – ITT population



Relationship between plasma concentration and effect

Dosing of the insulin glargine/lixisenatide combination is intended to be based on the patient's individual FPG values. The respective dose of lixisenatide will therefore be determined by the insulin glargine dose and the insulin glargine/lixisenatide ratio. No individual adjustment for glycaemia control of the lixisenatide dose will be performed. Therefore, no PK/PD relationship of the combination was required for assessing dose recommendations.

The PK/PD relationship of insulin glargine 100 U/mL monotherapy was analysed as a secondary endpoint in the multiple dosing study TDR11626. Scatter plots of individual GIR-AUC_{0-24h} over INS-AUC_{0-24} by treatment showed a positive correlation between the GIR-AUC and INS-AUC over the dosing interval. In steady state, a trend for higher GIR-AUC at higher exposure (INS-AUC_{0-24}) was observed.

For lixisenatide monotherapy, using mixed-effects modelling and an earlier population PK model for lixisenatide, the effect of lixisenatide on plasma glucose concentrations in patients with T2DM was investigated for FPG and PPG, using data pooled from Phase 2 studies PDY6797 and DRI6012.

The FPG model applied to responders described the effect of lixisenatide as a reduction in glucose production in a turnover model. The glucose production rate was reduced, following the lixisenatide concentration according to an E_{max} model. The maximum reduction in glucose production rate was estimated to be approximately 44%. The characteristic time constant of the influence of lixisenatide in this process was approximately 29 hours. The EC_{50} was 18.5 pg/mL, with a high variability. Baseline FPG (i.e., before start of treatment) and Asian race were covariates for EC_{50}.

The maximum effect of lixisenatide on plasma glucose $AUC_{0.5-4.5h}$ after a standard breakfast (PPG) was a reduction of 320.4 mg.h/dL (17.8 mmol.h/L) for the population mean, compared with no lixisenatide treatment. The lixisenatide AUC_{50} (where half of the effect was observed) was approximately 104 pg.h/mL (95% CI: 57 to 151 pg.h/mL).

To evaluate the effect of a decrease in C_{max} by 16% of lixisenatide at unchanged exposure when administered as insulin glargine/lixisenatide combination compared to lixisenatide alone (Study BDR11578), simulations were performed applying the population PK/PD model describing the correlation between lixisenatide concentration and effect on FPG.

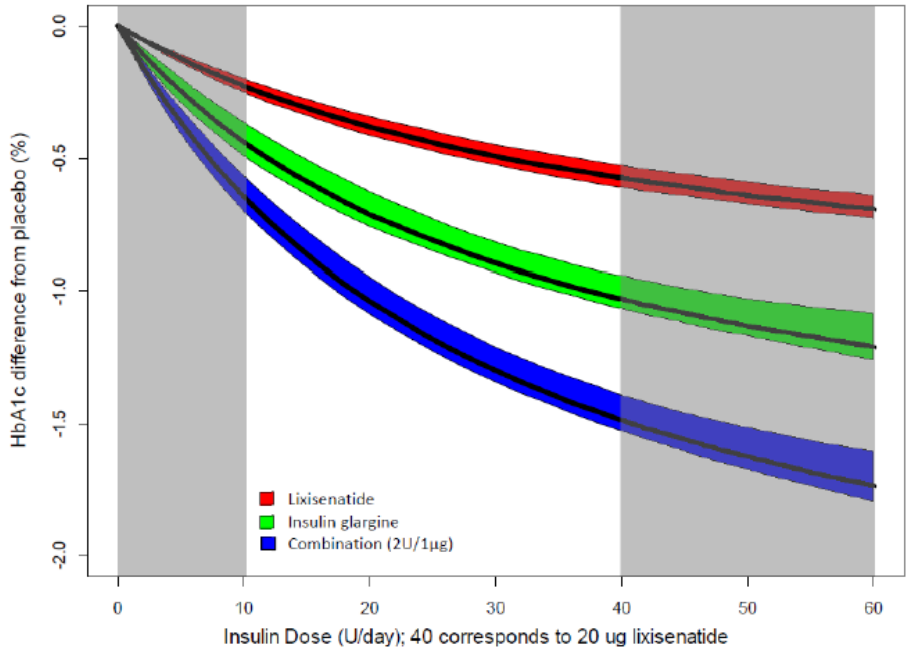
The decrease in C_{max} by 16% was simulated by decreasing the absorption rate constant k_a by 23%. Due to the flip-flop kinetics of lixisenatide, this decrease in k_a resulted in a simulated prolonged exposure to lixisenatide. The simulation suggested an improved effect of lixisenatide on FPG indicating that the time of exposure to lixisenatide rather than maximum concentration determines the efficacy. This conclusion is further supported by that fact that C_{max} of lixisenatide following administration of the insulin glargine/lixisenatide combination is well above the EC_{50} value of 10.3 pg/mL in the population PK/PD base model.

Modelling of interaction between insulin and GLP-1 analogues

A longitudinal model-based meta-analyses (MBMA) was performed to quantify the HbA1c response to treatment with different basal insulins in combination with different GLP-1 analogues. There was a statistically significant interaction between GLP-1 analogues and basal insulins such that the effect of the combination was synergistic but less than the sum of the two independent effects. The interaction coefficient was found to be similar and not statistically significantly different for the interaction between insulin glargine and lixisenatide vs insulin degludec and liraglutide

Based on the model, the dose-response for lixisenatide monotherapy, insulin glargine monotherapy, and the fixed ratio combination at a ratio of 2U/1µg at 24 weeks in a typical population on an oral antidiabetic drug (OAD) background therapy with a mean baseline HbA1c of 8% was estimated (Figure 2). The black lines are the mean estimated effects and the coloured regions span the 90% CI. The figure shows that the response of the combination is greater than each of the individual components over the complete dose range, consistent with the synergistic interaction. A comparison of the dose-response for lixisenatide monotherapy and contribution of lixisenatide to the response of fixed ratio combination at a ratio of 2:1 (Pen A in the dose ranges of 10 to 40 U insulin glargine and 5 to 20 µg lixisenatide) showed that there is a significant contribution of the individual components to the fixed ratio combination over the complete dose range. At low doses the contribution of lixisenatide to the fixed ratio combination is almost as large as the independent effect of lixisenatide.

Figure 2 Estimated dose-response for lixisenatide monotherapy, insulin glargine monotherapy, and the combination therapy (Pen A)



Grey areas indicate dose ranges outside the intended dose range of Pen A (10 to 40 U insulin glargine and 5 to 20 µg lixisenatide).
The x-axis shows the dose of insulin glargine. The lixisenatide dose can be obtained by dividing the insulin glargine dose by 2.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The applicant wants to bridge to the clinical pharmacology data for the mono-components, based on showing similar exposure to the mono-components given as separate injections. For a fixed-dose combination containing known active substances the Guideline on clinical development of fixed combination medicinal products states that bioequivalence should be demonstrated between the free combination of the individual mono-components and the marketing formulation (fixed combination). However, since the indication is not a substitution indication and since the final formulation of the fixed combination was used in the phase 3 studies, it is not considered critical to demonstrate formal bioequivalence between the fixed combinations and the free combination. The applicant states that the objective of the phase 1 program was not to demonstrate bioequivalence to the mono-components but to characterize the PK and PD of lixisenatide when administered as combination compared to separate simultaneous injections. This is agreed.

The method for detection of lixisenatide was considered sufficiently validated during the assessment of Lyxumia. The performed re-validations due to extension of calibration range and change of laboratory are adequate. The performance of the analytical methods for insulin glargine was acceptable. The method is not selective for insulin glargine but also measures human insulin as well as metabolites M1 and M2. The performance of the analytical methods for anti-lixisenatide and anti-insulin antibodies seems acceptable.

Absorption

Study **BDR10880** is considered to be the most important study, since it investigated the pharmacokinetics of insulin glargine and lixisenatide as a fixed ratio combination compared to the pharmacokinetics of each substance administered as separate simultaneous injections at two different fixed ratios (1.5 U/1 µg and 4 U/1 µg), covering the range of ratios intended for marketing. The formulations tested in study BDR10880 were not of the same fixed ratio concentrations as those intended for marketing, but the ratios intended for marketing (2 U/1 µg and 3 U/1 µg) are within the range of ratios tested in the study. For insulin glargine, the same concentration (100 U/ml) is used in study BDR10880 as well as in the formulations intended for marketing. This comparison is considered sufficient since the indication is not a substitution indication and since the final formulation of the fixed combination was used in the phase 3 studies. The study was performed in patients with type 1 diabetes mellitus (lacking an endogenous source of insulin) since the bioanalytical method used for assessment of insulin glargine showed complete cross-reactivity to human insulin. For lixisenatide, the total exposure (AUC_{inf}) almost met the equivalence criteria for strength 1 (ratio 0.92, 90% CI 0.78-1.08) and did meet the equivalence criteria for strength 2 (ratio 0.97, 90% CI 0.83-1.13) when comparing the premixed combination to separate simultaneous injections. For AUC_{0-t} the results were not within formal acceptance criteria (strength 1 ratio 0.82, 90% CI 0.68-0.99 and strength 2 ratio 0.93, 90% CI 0.77-1.11). The results however indicate similar total exposure of lixisenatide with the fixed combination compared to the free combination although not all comparisons are within formal equivalence criteria. Regarding C_{max}, the fixed ratio combination resulted in lower values compared to the separate simultaneous injections (34 % lower C_{max} with strength 1 and 22% lower C_{max} with strength 2). T_{max} was achieved 1 hour later for strength 1 and 0.75 hour later for strength 2 compared to the reference. The applicant has included a discussion regarding the effect of a decrease in lixisenatide C_{max} at unchanged exposure using simulations with a previously developed population PK/PD-model, concluding that this decrease is not clinically relevant. It is agreed that a decrease in lixisenatide C_{max} of 22-34% is not likely to be clinically relevant considering the available data on efficacy and safety for lixisenatide, the fact that the product is individually titrated based on blood glucose levels and considering that the final combination formulation has been used in the phase 3 studies.

For insulin glargine the point estimates for $AUC_{0-24\,h}$ were 0.86 (90% CI 0.77-0.96) and 0.88 (90% CI 0.79-0.98) for the treatment ratios T1/R1 and T2/R2 respectively. Thus, formal equivalence was not demonstrated since the lower limit of the confidence interval was slightly below 0.80. A 12-14% decrease in AUC_{0-24h} for insulin glargine was seen when given as a fixed ratio combination with lixisenatide compared to as separate simultaneous injections. However, the relative bioavailability of insulin glargine can be considered to be comparable in the fixed ratio combination compared to separate simultaneous injections. Since insulin glargine does not have a distinguished peak following subcutaneous injection it is considered acceptable to only calculate ratios and confidence intervals for AUC and not for c_{max} for insulin glargine.

It is not intended for patients to be able to switch between separate administrations of the individual components and the combination, and thus it is not necessary to show strict bioequivalence.

Study **BDR12457** investigated the relative bioavailability of lixisenatide when administered in combination with insulin glargine at three different fixed ratios (0.5 U/1 µg, 1U/ 1µg and 2U/1 µg), i e without comparison to the individual mono-components. One of the ratios tested was 2 IU/1 µg, which is one of the ratios intended for

marketing. All treatments tested resulted in similar exposure to lixisenatide. Thus, the bioavailability of lixisenatide was not affected by the insulin glargine/lixisenatide ratio.

Study **BDR11578** investigated high body-weight adjusted doses of insulin together with a fixed dose of lixisenatide, i.e. not as a fixed ratio combination, but with a range of ratios relevant the formulations intended for marketing. The exposure of insulin glargine as well as of lixisenatide was within conventional bioequivalence criteria when comparing administration of the on-site mix to separate simultaneous injections, while the C_{max} of lixisenatide was 16 % lower and the t_{max} occurred slightly later. The results are largely in line with the results from study BDR10880 with the fixed-ratio combination.

Study **BDR11540** investigated low doses of insulin together with a fixed dose of lixisenatide, but the formulations were given as fixed-ratio combinations of 0.25U/1µg and 0.5 U/1 µg (i.e. outside the range of ratios intended for marketing). In contrast to the previous pharmacokinetic studies, this study had treatment with only lixisenatide as reference (not separate injections of both insulin glargine and lixisenatide). The two test treatments were bioequivalent to each other, in line with the results from study BDR12547. However, administration of lixisenatide together with insulin glargine resulted in significantly lower exposure compared to administration of lixisenatide alone. The test formulations had 35-40% lower AUC and 46-48% lower C_{max} compared to the reference treatment. See further discussion in section on interactions.

Study **BDR11038** and **PKD12406** investigated other insulin glargine concentrations than the concentration intended for marketing, and has therefore not been assessed. However, since study PKD12406 was the only study except study BDR11540 where the fixed ratio combination was compared to lixisenatide monotherapy, this study has been briefly summarised. In contrast to the results from study BDR11540, study PKD12406 indicated similar total exposure with the fixed combination compared to lixisenatide monotherapy. This is in line with what has been seen when comparing the fixed combination to separate simultaneous injections of the mono-components.

Given the similarity in PK of the two components when given separately or together, a major difference on the influence of injection site between the fixed combination and the mono-components is not expected. Also, for a long-acting product differences in rate of absorption are generally not very critical. Since the mono-components can be administered in thigh, abdomen or upper arm without clinically relevant differences in PK and since the patients could select between these injections sites in the phase 3 studies for the combination, it is considered acceptable that the effect of site on injection has not been specifically investigated for Suliqua. As for many subcutaneous formulations, there could be a risk for higher intra-individual variability in exposure in patients with high BMI alternating between injection sites with more or less subcutaneous fat. In this case, the clinical impact of the variation is however expected to be low, considering the long-acting nature of both components together with the relatively high between-day variability in food intake and physical exercise of most patients.

Distribution

Vz/F of lixisenatide reported from studies with the fixed ratio combination was similar to results previously obtained with the mono-component. For insulin glargine, no information regarding distribution volume or protein binding is given in the SmPC or EPAR. No new studies regarding the distribution of the fixed combination are necessary.

Elimination

It is agreed that no new studies on the metabolism or excretion of lixisenatide or insulin glargine are warranted. Pharmacokinetic data for the mono-components are referred to. This is sufficient.

Dose-proportionality and time-dependency

For lixisenatide, the results regarding dose-proportionality with the combination are line with the results for the mono-component which has demonstrated roughly dose-proportional increase in exposure. For insulin glargine the results with the combination indicate dose-proportional increase in exposure, although based on a between-study comparison. It is agreed that no relevant accumulation of lixisenatide or insulin glargine is to be expected when given in combination.

Intra- and inter-individual variability

The inter-individual variability seen with the fixed ratio combination was moderate and in line with what has been seen for the mono-components.

Pharmacokinetics in target population

Sparse sampling was performed in the phase 2 and 3 studies, but except for the assessment of the effect of anti-lixisenatide antibodies on lixisenatide PK in the phase 2 study (see Special populations), the applicant has not discussed this data in the Summary of Clinical Pharmacology studies. Since the concentration data reported in the phase 3 studies have not been corrected for administered dose it is difficult to draw any conclusions from this information. However, considering the minor effects of the PK of lixisenatide and insulin glargine in the fixed ratio combination compared to the mono-components and since data with the mono-components indicate similar exposure in T2DM patients as in healthy volunteers, no additional PK data in the target population is considered necessary.

Special populations

No specific studies have been performed in special populations with the new combination except regarding influence of anti-lixisenatide antibodies. The results with the fixed ratio combination are in line with data for the mono-component, i.e. that following single dose administration the PK profiles of antibody-positive subjects was within the range found for antibody-negative subjects, but following multiple-dose administration there was a marked increase in exposure in antibody-positive subjects. No additional data on special populations with the combination is necessary. The information regarding special populations in the suggested SmPC reflects the information from the SmPCs for the mono-components.

Interactions

Data from the mono-components are referred to, with a discussion regarding the lower C_{max} and later t_{max} observed for the combination product on the effect of gastric emptying.

It is agreed that no interaction between circulating insulin glargine and lixisenatide is expected. However, in study BDR11540, where the fixed combination was compared to lixisenatide monotherapy, the exposure of lixisenatide was significantly lower with the fixed combination, while comparisons with separate simultaneous injections of the mono-components in other studies showed similar exposure of lixisenatide. This might indicate that insulin glargine affects lixisenatide exposure due to some other mechanism than by interaction during the absorption following subcutaneous injection. In contrast, study PKD12406 did not indicate that the lixisenatide exposure would be lower with the fixed combination compared to lixisenatide monotherapy. It is noted that the dose-corrected exposure of lixisenatide from the fixed combination appears to be lower in study BDR11540 than in the other submitted studies. The reasons for the decreased lixisenatide exposure observed in study BDR11540 has not been elucidated, but seems to be an isolated case as compared to the results from the other studies and is judged as not critical.

The applicant has agreed to include the same recommendations in the SmPC regarding administration time of coadministered drugs as for Lyxumia, i.e. that medicinal products that are particularly dependent on threshold concentrations for efficacy and gastro-resistant formulations should be taken at least 1 hour before or 4 hours after lixisenatide injection. Although gastric emptying has not returned to normal by 4 hours after administration of 20 microgram lixisenatide (given as monotherapy or as fixed-dose combination) the effect on C_{max} seen on orally administered drugs taken 4 hours after administration of lixisenatide was considered not clinically relevant during the assessment of Lyxumia. When given as the fixed-dose combination, it seems to take some additional time for the gastric emptying to return to normal compared to monotherapy, but this difference is not considered large enough to warrant changes in the SmPC compared to Luxymia.

Pharmacodynamics

The insulin glargine/lixisenatide combination is a fixed ratio combination product of a long-acting human insulin analogue (insulin glargine) together with a glucagon like peptide-1 (GLP-1) receptor agonist (lixisenatide). Since both insulin glargine and lixisenatide are efficacious when given once-daily, both components can be mixed as a defined fixed ratio formulation to be delivered by one single injection combining the complementary therapeutic benefits of the constituent agents.

The mechanisms of action for insulin glargine and lixisenatide are well known and no new data have been provided. The mechanism of action for lixisenatide is complementary to the mechanism of action of insulin glargine with regards to the glucose lowering effect.

Only one adequately sized PD study (BDR10880) was performed which investigated whether the pharmacodynamics of insulin glargine was affected when given in two different fixed combinations with lixisenatide as compared to single injections. The study was conducted in patients with T1DM. No significant differences were observed with regards to GIR-AUC_{0-24h} or GIR_{max}. The impact of the combination on the pharmacodynamics of lixisenatide was not investigated. These data were supported by a smaller preliminary study which also was conducted in T1DM patients.

The primary pharmacology of insulin glargine has been well characterised within the original MAA and was not further investigated with this application.

The primary pharmacology of lixisenatide has also been well characterised. Data from the lixisenatide monotherapy studies PDY12545, ACT6011 and DRI6012 provide supplementary information on the mode of action as well as the pharmacodynamic effects of lixisenatide at doses below 20 µg. In addition to effects of lixisenatide on glucagon and glucose-induced insulin secretion, a significant effect on gastric emptying has been shown for the dose range 5 to 20 µg. According the Applicant, the delay in gastric emptying observed with lixisenatide is an important contributor to the effect of lixisenatide on PPG.

With the FRC, the lowest dose of lixisenatide administered is 5 µg lixisenatide once-daily. Study DRI6012 investigated the dose range 5-30 µg lixisenatide and a statistically significant effect on change from baseline HbA1c, compared to placebo, was observed for all doses. The magnitude of effect was comparable for the 5 and 10 µg dose, the latter being the recommended starting dose for lixisenatide when used as monotherapy.

Since dosing of the insulin glargine/lixisenatide combination is to be based on the patient's individual FPG values, the respective dose of lixisenatide will be determined by the insulin glargine dose and the insulin glargine/lixisenatide ratio. Therefore, no PK/PD relationship of the combination is required for assessing dose recommendations.

For both insulin glargine and lixisenatide, the relationship between plasma concentration and effect has been established.

To evaluate the effect of a decrease in C_{max} by 16% of lixisenatide at unchanged exposure when administered as insulin glargine/lixisenatide combination compared to lixisenatide alone (Study BDR11578), simulations were performed applying the population PK/PD model describing the correlation between lixisenatide concentration and effect on FPG. The simulation suggested an improved effect of lixisenatide on FPG indicating that the time of exposure to lixisenatide rather than maximum concentration determines the efficacy. As discussed in the Pharmacokinetics AR, a reduction in lixisenatide C_{max} of 22-34% when given as insulin glargine/lixisenatide combination compared to separate simultaneous injections as seen in study BDR10880 is considered more relevant than the decrease of 16% seen in study BDR11578. Thus, it would be more relevant to simulate the effect of a 22-34% decrease in C_{max}. However, considering the available data on efficacy and safety for lixisenatide, and considering that the final combination formulation was used in the phase 3 studies, a decrease in lixisenatide C_{max} of 22-34% is not considered clinically relevant.

A larger model based meta-analysis showed that the combination of lixisenatide and insulin glargine had a synergistic effect on the lowering of HbA1c. The magnitude of the synergistic effect was not different compared to the combination liraglutide and insulin degludec.

No data on secondary pharmacology, PD interactions or genetic differences have been provided. As both components are well characterised with regards to secondary effects and no important interactions or differences in PD due to genetic differences are expected, this is acceptable.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic documentation for the new combination is sufficient. The bioavailability of insulin glargine and lixisenatide in the new formulation has been sufficiently characterised, and bridging to clinical pharmacology data of the mono-components is acceptable.

The pharmacodynamic documentation for the new combination is considered sufficient. Data has been provided that could justify the use of a lower initial dose of lixisenatide (5 µg) than currently approved, when initiating treatment.

2.4.6. Clinical efficacy

Dose-response studies and main clinical studies

The development program recruited patients with T2DM, including patients insufficiently controlled on one or more OADS or insufficiently controlled on basal insulin ± 1 to 2 OADs. The efficacy of the fixed-ratio combination in patients with T2DM was assessed in 2229 randomized patients in one Phase 2 proof-of-concept study and two pivotal Phase 3 studies (Table 2).

Dose-response studies

No dose response study was performed. In the following the Applicant's rationale for the dose selection for the fixed-ratio combination is given.

Dose selection rationale for the fixed-ratio combination

The majority of the target population for the FRC is expected to require a daily dose of insulin glargine between 10 to 60 U. In order to cover the range of 10 to 60 U of insulin glargine while limiting the maximum lixisenatide dose to 20 µg, two pens with two different fixed ratios and dose-ranges were used in the Phase 3 studies (Figure 3). The lower end of the lixisenatide dose range is the minimum dose for glycaemic efficacy as defined in the

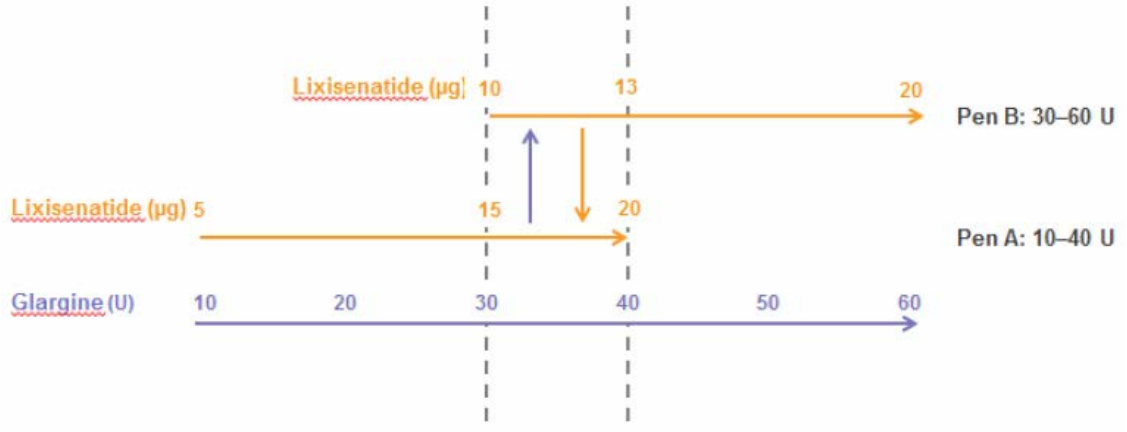
Phase 2 dose-ranging Study DRI6012 (N=542) where once daily prandial doses from 5 to 20 µg provided significantly better HbA1c and PPG reductions than placebo in patients with T2DM.

The formulation of the FRC used in the Phase 3 studies is identical to the proposed commercial formulation. The FRC is provided in a pre-filled disposable SoloStar pen-injector.

Dosing concept

The rationale for developing the selected ratios of insulin glargine and lixisenatide was to optimize the dose-range of insulin glargine and concomitantly deliver an effective dose of lixisenatide up to its maximum approved dose (20 µg) as detailed below. This requires that the FRC is available in 2 different dose ratios (Figure 3).

Figure 3 Fixed-ratio combination of lixisenatide and insulin glargine in Pen A and Pen B



- Pen A (10 - 40 prefilled pen, peach) contains a sterile solution with 100 U/mL insulin glargine (Lantus, 100 U/mL) and 50 µg/mL lixisenatide in a ratio of 2 U insulin glargine/1 µg lixisenatide, so that each unit of insulin glargine is given with 0.5 µg of lixisenatide. The pen delivers doses from 10 to 40 U in steps of 1 unit, allowing administration of FRC doses between 10 U/5 µg and 40 U/20 µg.
- Pen B (30 - 60 prefilled pen, olive) contains a sterile solution with 100 U/mL insulin glargine (Lantus, 100 U/mL) and 33 µg/mL lixisenatide in a ratio of 3 U insulin glargine/1 µg lixisenatide, so that each unit of insulin glargine is given with 0.33 µg of lixisenatide. The pen delivers doses from 30 to 60 U in steps of 1 unit, allowing administration of FRC doses between 30 U/10 µg and 60 U/20 µg.

Treatment Initiation:

The dose at initiation is primarily based on the approach to use the appropriate insulin dose, without exceeding the approved lixisenatide starting dose.

- Insulin-naïve patients initiate treatment at a recommended daily insulin glargine dose of 10 U with a corresponding dose of 5 µg of lixisenatide.
- In patients switching from basal insulin to the FRC, different starting doses are available depending on previous insulin need: either Pen A (20 U/10 µg or 10 U/5 µg) or Pen B (30 U/10 µg), thereby avoiding a major decrease in their current insulin dose. During titration and maintenance: After initiation of the FRC and during titration, Pen A is used for total daily doses of 10 to 40 U and Pen B for total daily doses of 41 to 60 U.

- For a given daily dose between 30 and 40 units where there is an overlap between Pen A and Pen B (Figure 3), the pen which provides the higher dose of lixisenatide (Pen A) is to be chosen as long as it is well tolerated. Otherwise (e.g., persistent nausea and/or vomiting), Pen B can be used. For example, in the case of persistent GI effects, when a 30 to 40 U daily dose is administered with Pen A (with a corresponding lixisenatide dose of 15 to 20 µg), switching to Pen B may allow better GI tolerability: while maintaining the same insulin dose, the corresponding doses of lixisenatide is reduced to 10 to 13 µg.

The FRC dose is adjusted individually based on the patient's daily insulin glargine need. Only the dose of insulin glargine appears in the pen dosing window. The dose of lixisenatide follows the insulin glargine dose according to the chosen fixed-ratio. The human factors studies conducted for the FRC pens confirmed that the information provided to users about this dosing concept is understandable and helpful for the intended users to know the drug combination contained in each pen.

Main studies

The efficacy of the fixed-ratio combination was assessed in two pivotal phase 3 studies.

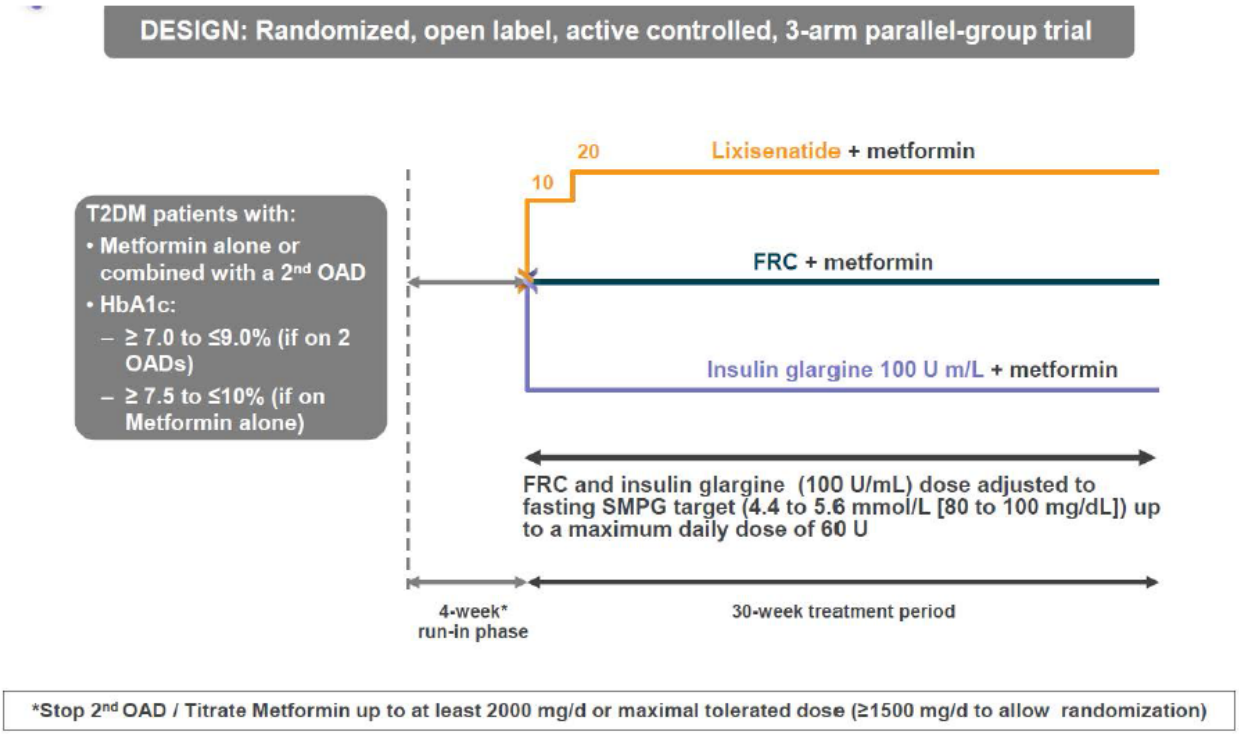
EFC12404 (LixiLan-O): A randomised 30 week, active-controlled, open-label, 3-treatment arm, parallel-group multicentre study comparing the efficacy and safety of insulin glargine/lixisenatide fixed ratio combination to insulin glargine alone and to lixisenatide alone on top of metformin in patients with T2DM.

EFC12405 (LixiLan-L): A randomised, 30-week, active-controlled, open label, 2-treatment arm, parallel group, multicentre study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination to insulin glargine with or without metformin in patients with T2DM.

Methods

Study EFC12404

Figure 4 EFC12404 study design



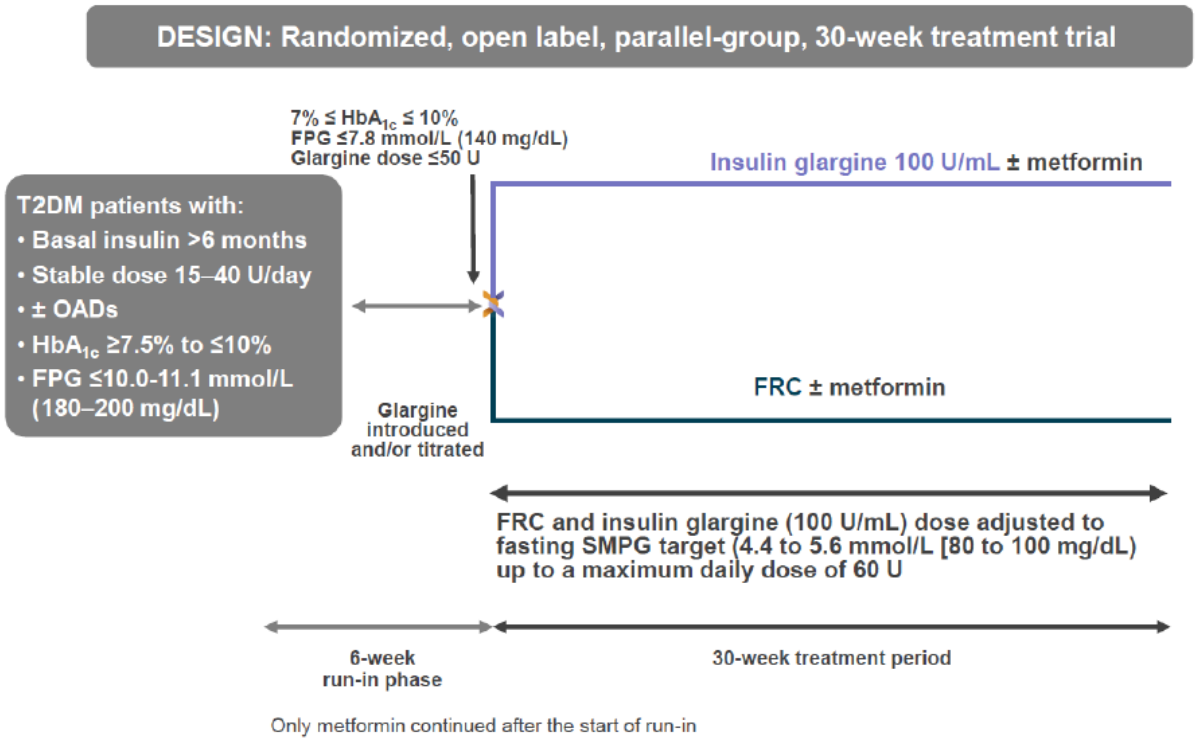
The study comprised 3 periods:

- An up to 6-week screening period, which included up to 2-week screening phase and a 4-week run-in phase, where sulfonylurea (SU), glinides, sodium-glucose cotransporter-2 SGLT-2 inhibitors, or dipeptidyl peptidase-4 (DPP-4) inhibitors if previously taken were discontinued and metformin treatment was optimized up to a daily dose of at least 2000 mg or up to the maximum tolerated dose (≥1500 mg/day)
- A 30-week open-label randomised treatment period
- A 3-day posttreatment safety follow-up period

The maximum study duration per patient was approximately 37 weeks.

Study EFC12405

Figure 5 EFC12405 study design



The study comprised 3 periods:

- An up to 8-week screening period, which included:
  - An up to 2-week screening phase. The run-in visit could be performed less than 2 weeks after the screening visit if the laboratory data were available.
  - A 6-week run-in phase with switch to (if appropriate) and/or dose titration/stabilization of insulin glargine, continuation of metformin (if appropriate), and discontinuation of sulfonylurea (SU), glinides, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, or dipeptidyl-peptidase-4 (DPP-4) inhibitors if previously taken at Visit 2.
- A 30-week open-label randomized treatment period
- A 3-day post-treatment safety follow-up period
- The maximum study duration per patient was approximately 39 weeks.

Study participants

Both studies included patients with T2DM diagnosed for at least 1 year before the screening visit.

Study **EFC12404** included insulin-naïve patients inadequately controlled on metformin ± a second OAD (at least 3 months of treatment). Inclusion criteria at the end of the 4-week run-in period were HbA1c ≥7% and ≤10%, FPG ≤ 13.9 mmol/L (≤250 mg/dL), and a maximum tolerated metformin dose of ≥1500 mg/day.

Study **EFC12405** included insulin-treated patients inadequately controlled on established basal insulin (at least 6 months) ± 1 to 2 OADs. Inclusion criteria at the end of the 6-week run-in were HbA1c ≥7% and ≤10%, mean

SMPG for the 7 days prior to randomization of ≤7.8 mmol/L (≤140 mg/dL), and an average insulin glargine daily dose ≥20 U and ≤50 U.

Exclusion criteria related to the safety of patients are detailed in the individual clinical study reports. Major criteria were related to a history of metabolic complications of diabetes or standard exclusion criteria for the GLP-1 receptor agonist class (amylase or lipase levels >3 upper limit of normal), history of pancreatic disease, or a calcitonin level ≥20 pg/mL [≥5.9 pmol/L].

Patients with a recent (within 6 months of study entry) history of stroke, myocardial infarction, unstable angina, or heart failure requiring hospitalization were excluded. Patients with inadequately controlled hypertension (i.e., systolic blood pressure >180 mmHg or diastolic blood pressure >95 mmHg) were also excluded. Haemoglobinopathy and haemolytic anaemia were also exclusion criteria since these conditions are known to potentially affect the evaluation of HbA1c levels.

Any contraindication to metformin use, according to local labelling (e.g., renal impairment defined as creatinine >1.4 mg/dL in women, >1.5 mg/dL in men, or creatinine clearance <60 mL/min) was exclusionary for all patients in Study EFC12404 where metformin was a mandatory background therapy and for those patients taking metformin in Study EFC12405.

Treatments

Patients in each study were provided with protocol-specified training on the pen-injector devices, treatment schedules, and dosing algorithms.

Fixed-ratio combination treatment group

The FRC was administered subcutaneously once daily (QD) within 1 hour before breakfast. The FRC dose was individualized based on clinical response and was titrated based on the patient's need for insulin (Table 8).

In study **EFC12404** (patients insufficiently controlled on metformin with or without a second OAD), the recommended daily starting dose of insulin glargine in insulin-naïve patients is 10 U. Therefore, the daily starting dose of the FRC in patients inadequately controlled on OADs was 10 U of insulin glargine/5 µg of lixisenatide. This daily dose was maintained during the first week of treatment.

In study **EFC12405** (patients insufficiently controlled on basal insulin ± 1 to 2 OADs), the recommended starting dose of lixisenatide when given as a separate injection is 10 µg once daily to be kept stable for 2 weeks. Therefore, patients switching from basal insulin to the FRC began treatment at a recommended daily lixisenatide dose of 10 µg using either Pen A (20 U glargine) or Pen B (30 U) depending on the insulin glargine dose received on the day before randomization as follows:

- If this dose was <30 U, the starting dose of the FRC was 20 U/10 µg (given with Pen A).
- If this dose was ≥30 U, the starting dose of the FRC was 30 U/10 µg (given with Pen B).

During titration, the choice of Pen A or Pen B was based on the required FRC daily dose: Pen A was to be used for daily doses below 40 U and Pen B for doses between 41 and 60 U. In EFC12404, patients needing a daily dose of more than 40 U were to be switched to Pen B which delivered doses up to 60 U. In EFC12405, patients who initiated treatment with Pen A but subsequently needed a daily insulin dose of more than 40 U were to be switched to Pen B.

The maximum daily dose was 60 U/20 µg. If a daily dose of the FRC >60 U/20 µg was needed to maintain FPG or HbA1c below thresholds defined for rescue therapy, the dose was to be kept at 60 U/20 µg and a rescue therapy initiated.

Insulin glargine

Insulin glargine (Lantus) is a marketed product and the dose used in this study was in accordance with its labelling documents. Doses could be set from 1 to 80 U in steps of 1 U. The fasting SMPG targets, the titration algorithm, and titration monitoring were the same as those for the FRC (Table 8).

In study **EFC12404** (patients inadequately controlled on metformin with or without a second OAD), the starting dose was 10 U. This daily dose was maintained during the first week of treatment.

In study **EFC12405** (patients inadequately controlled on basal insulin ± 1 to 2 OADs), patients already treated with insulin glargine entered the run-in phase with the same dose they received prior to screening. Patients receiving a different basal insulin were switched to insulin glargine. Doses were adjusted based on daily measured fasting SMPG in order to improve fasting glycaemic control and obtain mean fasting SMPG ≤7.8 mmol/L (≤140 mg/dL) measured for 7 days before the randomization visit, while avoiding hypoglycaemia. The titration procedure was at the discretion of the investigator.

During the randomized treatment period, patients randomized to insulin glargine had to administer the same daily dose on the day of randomization as the day before randomization. Subsequently, the dose was titrated once a week using the same algorithm as used for the FRC group (Table 8).

As the maximum daily dose of FRC was 60 U/20 µg, the comparative insulin glargine stand-alone dose was, in both study **EFC12404** and study **EFC12405**, capped at 60 U to best assess the contribution of the lixisenatide component to glycaemic control.

Lixisenatide treatment group (Study **EFC12404** only)

Lixisenatide was self-injected once daily with a pre-filled disposable pen, available for 2 different dose strengths of 10 µg (at initiation) and 20 µg (for maintenance). The injection time-point (before breakfast or dinner) was determined at the discretion of patient and investigator at randomization and had to be maintained until the end of the treatment period.

Lixisenatide was initiated with QD injections of 10 µg for 2 weeks. The lixisenatide dose was then increased to a maintenance dose of 20 µg QD from Week 2 through the end of the treatment period. If the maintenance dose of 20 µg QD was not tolerated, the lixisenatide dose could be reduced to 10 µg QD.

Titration of FRC and insulin glargine

In each pivotal study, the FRC and insulin glargine treatments were both titrated to a fasting SMPG target of 4.4 mmol/L to 5.6 mmol/L (80 to100 mg/dL), inclusive, in a treat-to target approach with once-weekly titration. Dose changes were based on the median of fasting SMPG values from the previous 3 days, measured by patients using glucometers and accessories supplied by the Sponsor, according to Table 8.

Table 8 Dose adjustment algorithm for FRC and insulin glargine

Median of fasting SMPG values from the last 3 days	Dose change (U/day)
>7.8 mmol/L (>140 mg/dL)	+4
>5.6 mmol/L and ≤7.8 mmol/L (>100 and ≤140 mg/dL)	+2
4.4 mmol/L to 5.6 mmol/L (80 to 100 mg/dL)	No change
≥3.3 mmol/L and <4.4 mmol/L (≥60 and <80 mg/dL)	-2
<3.3 mmol/L (<60 mg/dL) or occurrence of ≥2 symptomatic hypoglycemia or one severe hypoglycemia in the preceding week	-2 to -4 or at the discretion of the Investigator or medically qualified designee

SMPG = self-monitored plasma glucose

Titration monitoring was performed to ensure that the protocol-defined insulin dose adjustment algorithm was being followed.

Rescue therapy

Routine fasting SMPG and central laboratory alerts on FPG and HbA1c levels were used to ensure that glycaemic parameters remained below predefined rescue thresholds as defined in the protocols.

In the case of an FPG or HbA1c level above the protocol-defined thresholds, where no explanation was found and/or appropriate actions failed, or if a FRC dose >60 U/20 µg or an insulin glargine dose >60 U was necessary to decrease FPG or HbA1c levels to below the predefined thresholds, addition of a rescue therapy was recommended.

For the FRC and insulin glargine treatment groups in both studies, the recommended rescue therapy was the addition of short/rapid acting insulin (insulin glulisine when available) to be started as a single daily dose given at the main meal of the day (except breakfast in the FRC group). For the lixisenatide group in study **EFC12404**, the choice was at the investigator's discretion. No other GLP-1 receptor agonist, DPP-4 inhibitor, or basal insulin was allowed as rescue therapy in any of the treatment groups in either study.

Objectives

Study EFC12404

The primary objectives of this study were to demonstrate the superiority of the FRC to lixisenatide in HbA1c change from baseline to Week 30, and to demonstrate the noninferiority of the FRC to insulin glargine in HbA1c change from baseline to Week 30. If noninferiority was shown, statistical superiority of the FRC compared to insulin glargine on HbA1c change from baseline to Week 30 was to be tested according to the pre-specified testing hierarchy.

Study EFC12405

The primary objective of this study was to demonstrate the superiority of the FRC to insulin glargine in HbA1c change from baseline to Week 30.

Outcomes / endpoints

The primary efficacy endpoint in both pivotal studies (**EFC12404** and **EFC12405**) was change in HbA1c from baseline to Week 30.

The secondary efficacy endpoints in both pivotal studies (**EFC12404** and **EFC12405**) were:

- Percentage of patients reaching HbA1c ≤6.5% at Week 30
- Percentage of patients reaching HbA1c <7% at Week 30
- Change in 2-hour PPG and plasma glucose excursion during a standardized meal test from baseline to Week 30 (for all patients in the FRC or insulin glargine groups and patients injecting IMP in the morning in the lixisenatide group); the same variables were also assessed at the 30-minutes and 1-hour time points
  Note: 30-minute, 1-hour, or 2-hour plasma glucose excursion = 30-minute, 1-hour, or 2-hour PPG value – plasma glucose value obtained 30 minutes prior to the start of meal and before IMP administration if IMP was injected before breakfast
- Change in body weight from baseline to Week 30
- Change in FPG from baseline to Week 30
- Change in 7-point SMPG profiles from baseline to Week 30 (each time point and average daily value)
- Percentage of patients reaching HbA1c <7% with no body weight gain at Week 30
- Percentage of patients reaching HbA1c <7% at Week 30 with no documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L] during the 30-week open-label treatment period)
- Percentage of patients reaching HbA1c <7% with no body weight gain at Week 30 and with no documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L]) during the 30-week open-label treatment period
- Percentage of patients requiring rescue therapy during the 30-week open-label treatment period

In study **EFC12404**, the insulin glargine dose at Week 30 (in the FRC group and insulin glargine group only) was included as a secondary endpoint, whereas change in daily dose of insulin glargine dose from baseline to Week 30, was included as a secondary endpoint in study **EFC12405**.

In both Phase 3 trials, documented symptomatic hypoglycaemia was defined by the protocol as an event during which typical symptoms of hypoglycaemia were accompanied by measured plasma glucose of ≤3.9 mmol/L (≤70 mg/dL). Severe symptomatic hypoglycaemia was defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Sample size

In both studies the sample size calculations were based on the primary efficacy variable change in HbA1c from baseline to week 30.

In study **EFC12404** the following assumptions were made:

- A common standard deviation of 1.1 %
- A true difference between FRC and insulin glargine of zero and a non-inferiority margin of 0.3 %
- A 0.4 % mean difference between FRC and lixisenatide
- A t-test at a 1-sided 2.5 % significance level with at least 95 % power

Based on these assumptions and a randomisation ratio of 2:2:1, 1125 patients were needed, 450 patients in the

FRC and insulin glargine arm respectively and 225 patients in the lixisenatide group.

In study **EFC12405**, 350 patients per group were needed assuming a mean difference between the FRC and insulin glargine of 0.4%, a common standard deviation of 1.1% and a t-test at a 2-sided 5% significance level with at least 95% power.

Randomisation

At the end of the screening period, eligible patients were centrally randomised (both studies) (using permuted block randomisation schedule) via an interactive voice/web response system (IVRS/IWRS).

In study **EFC12404** patients were randomised in a 2:2:1 ratio to FRC, insulin glargine or lixisenatide stratified by HbA1c value at visit 4 (week -1) (<8%, ≥8%) and second oral anti-diabetic drug (OAD) use at screening (yes, no).

In study **EFC12405** patients were randomised in a 1:1 ratio to FRC or insulin glargine, stratified by value of HbA1c at Visit 5 (Week -1) (<8%, ≥8%) and metformin use at screening (yes, no).

Blinding (masking)

Both studies were open-label because of differences in the type and number of pens used to administer the FRC, insulin glargine and, in study EFC12404, lixisenatide. Primary and key secondary efficacy endpoints (biochemical in nature) were measured in a central laboratory. The Investigator and the Sponsor were not to have any access to HbA1c data or to data of the standardized meal test endpoints obtained after the baseline visit until the end of the study.

The Data Monitoring Committee (DMC) received unblinded, closed reports from an independent statistician, to be handled strictly confidentially. Additional external and independent committees involved in the studies (ARAC, CAC and PSAC) reviewed and adjudicated events in a blinded manner.

Statistical methods

In both Phase 3 pivotal studies the statistical methodology was similar although differed with respect to non-inferiority/superiority testing of the primary efficacy endpoint and the order of hierarchical testing for the key secondary endpoints.

Primary superiority hypotheses, FRC vs lixisenatide (**EFC12404)** and FRC vs insulin glargine (**EFC12405**) respectively, was tested at a 2-sided 5% significance level. In study **EFC12404**, non-inferiority of the FRC vs insulin glargine was to have been demonstrated if the upper bound of the 2-sided 95% CI for the difference between the FRC and insulin glargine in change in HbA1c from baseline to week 30 was ≤0.3%.

Efficacy analyses were performed on the mITT population using all efficacy assessments collected during the study, including those obtained after IMP discontinuation or introduction of rescue therapy. It was initially planned to use only on-treatment data. This approach was changed in both studies through study protocol amendment 1 (dated 09 July 2014, EFC12404 and 03 July 2014, EFC12405).

The mITT population was defined as all randomised patients who had both a baseline assessment and at least one post-baseline assessment. The definition of the mITT was also changed with amendment 1 in that the requirement “received at least 1 dose of IMP” was removed.

The analyses of the primary endpoint were performed using a mixed-effect model with repeated measures (MMRM), under the missing at random framework. The MMRM model included treatment group, randomisation strata, visit, treatment-by-visit interaction and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. The key sensitivity analysis for the primary efficacy endpoint used the same MMRM model including only the scheduled HbA1c measurements collected during the on-treatment period (i.e., excluding HbA1c values collected after IMP discontinuation or the introduction of rescue therapy). Additional sensitivity analyses included e.g. an analysis of covariance (ANCOVA) with missing data imputed by the last observation carried forward (LOCF).

In both studies a step-down testing procedure was applied for the primary and a number of selected secondary endpoints in order to control the type I error. In study EFC12404 testing on secondary endpoints was to continue only when both co-primary hypotheses had been established. In study EFC12404 the step-down testing procedure also included a test of superiority, FRC vs insulin glargine, on the primary endpoint.

All continuous secondary efficacy endpoints were analysed using the same MMRM approach as used for primary analyses except for 30-minute, 1-hour, 2-hour PPG and plasma glucose excursion endpoints that was analysed using ANCOVA (LOCF). All categorical secondary efficacy endpoints were analysed using a stratified Cochran-Mantel-Haenszel test. Sensitivity analyses of selected secondary endpoints were performed using scheduled measurements collected during the on-treatment period (excluding those collected after introduction of rescue therapy).

A number of subgroup analyses were pre-planned. There was no formal efficacy interim analysis planned or performed in any of the two pivotal studies.

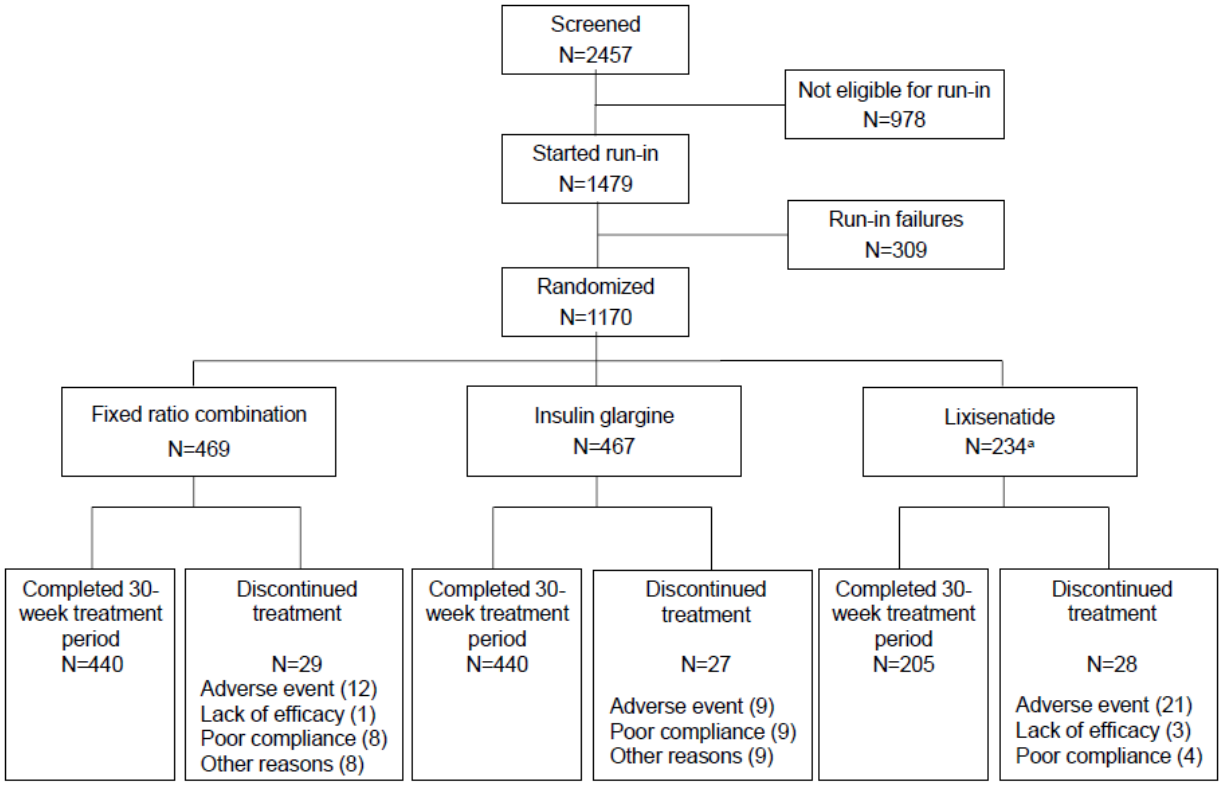
With the study protocol amendment 1 dated 09 July 2014 (EFC12404) and 03 July 2014 (EFC12405) a few additional statistical changes were implemented (besides those already mentioned above). They concerned e.g. the modification or adding of sensitivity analyses following the change in the primary analysis and in study EFC12404, a few changes with regard to the step-down testing procedure. In principal all changes made were due to health authority´s requests or comments.

The final version of the statistical analysis plan (SAP) for study EFC12404 was dated 12-Mar-2015 (version 2). The final version of the SAP for study EFC12405 was dated 13-Mar-2015 (version 2). A few analyses/summaries were added after database lock, in both studies post hoc analyses intended to be supportive were performed; key efficacy endpoints (e.g., HbA1c, 2-hour PPG excursions, and body weight) and documented symptomatic hypoglycaemia were also evaluated by final insulin and lixisenatide dose levels. According to both SAPs the database (for each of the study, respectively) was planned to be locked approximately 4 weeks after last patient last visit. No actual dates have been found. Considering that the latest version of both SAPs was dated before each of the studies were completed this is not considered to be an issue.–

Results - Study EFC12404

Participant flow

Figure 6 Study EFC12404: Patient disposition



[a] One patient was randomized to the lixisenatide group but did not receive open-label study treatment.

The percentage of patients completing the open-label on-treatment period in the FRC group (93.8%) was similar to the insulin glargine group (94.2%) and was higher than in the lixisenatide group (87.6%).

Conduct of the study

The clinical study protocol version 1 was dated 19 November 2013. There was one substantial protocol amendment dated 09 July 2014. Percentages of patients with major or critical efficacy deviations potentially impacting efficacy analyses were low and similar for the 3 treatment groups.

One site was closed due to non-compliance; the 5 patients concerned; 2 (0.4%) and 3 (0.6%) in the FRC and insulin glargine arm respectively, were transferred to another site (site 710005), and continued the study as planned. Due to the limited number of patients recruited at this site (5 of 1170 randomized patients), no sensitivity analyses were performed.

Baseline data

Baseline demographics were well-balanced across treatment groups. The overall population was balanced by gender and was predominantly Caucasian (90.1%) with a mean age of 58.4 years. The population had a mean baseline body mass index (BMI) of 31.7 overall (BMI range 19-42) and 63.4% of patients had a baseline BMI ≥30.0, indicating that the majority of the population was obese.

Medical history was generally similar for the 3 treatment groups. Almost all patients (97.1%) in the randomized population presented with at least 1 previous disease or history of surgery. The following SOCs were affected most frequently: vascular disorders (76.7%), metabolism and nutrition disorders (75.1%), and surgical and medical procedures (45.6%).

The majority of patients (88.2%) in the randomized population had a history of cerebrovascular events or cardiovascular risk factors, with hypertension being the most common (74.9% of patients) followed by dyslipidaemia (65.0% of patients).

Most patients (86.1%) did not smoke at screening and 53.1% of patients did not drink any alcohol in the last 12 months before screening.

A low percentage of patients (3.8%) had clinically significant abnormal physical examination findings at screening.

Screening and/or baseline characteristics related to diabetes were comparable in the 3 treatment groups and indicative of a population in poor glycaemic control that would benefit from insulin initiation. Overall, the mean duration of diabetes was 8.8 years with a mean HbA1c of 8.2% at screening. Metformin was a mandatory background therapy (mean daily dose at baseline: 2249.8 mg). Importantly, the majority of patients were using 2 OADs at screening (57.9%), with 53.9% using a sulfonylurea as second OAD at screening. For patients using 2 OADs, the overall mean duration of use was 4.2 years.

Numbers analysed

Of the 1170 randomised patients, 3 patients (1 patient from each treatment group) were excluded from the mITT population because they did not have any post baseline efficacy assessments.

One patient randomised to the lixisenatide group requested not to be treated and was excluded from the safety population.

Table 9 Study EFC12404: Analysis populations

	Fixed Ratio Combination	Insulin Glargine	Lixisenatide	All
Randomized population	469 (100%)	467 (100%)	234 (100%)	1170 (100%)
Efficacy population				
Modified Intent-to-Treat (mITT)	468 (99.8%)	466 (99.8%)	233 (99.6%)	1167 (99.7%)
Safety population	469	467	233	1169
PK population	466	0	222	688

Note: The safety population patients are tabulated according to treatment actually received (as treated).
For the efficacy population, patients are tabulated according to their randomized treatment.
There is no patient randomized in a group and taking another study treatment.

Outcomes and estimation

Primary endpoint - Mean change in HbA1c (%) from baseline to Week 30

The primary objectives of the study were met as the non-inferiority and then statistical superiority according to the pre-specified testing hierarchy of the FRC compared to insulin glargine on HbA1c change from baseline to Week 30 was demonstrated as well as statistical superiority of the FRC over lixisenatide.

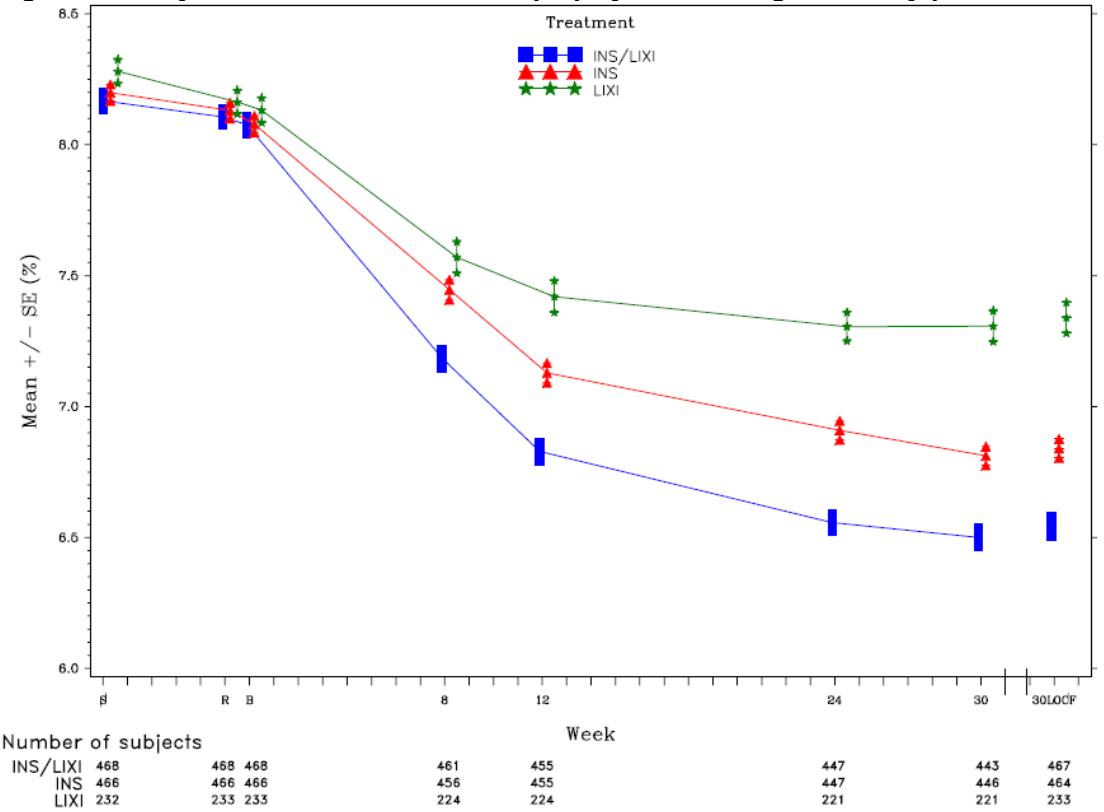
The changes from baseline to Week 30 in HbA1c were -1.63% for the FRC group, -1.34% for the insulin glargine group, and -0.85% for the lixisenatide group, reaching mean HbA1c values of 6.50%, 6.81%, and 7.31% at Week 30, respectively (Table 10).

Table 10 Study EFC12404: Mean change in HbA1c (%) from baseline to Week 30 using MMRM - mITT population

HbA1c(%)	Fixed Ratio Combination (N=468)	Insulin Glargine (N=466)	Lixisenatide (N=233)
Baseline			
Number	467	464	233
Mean (SD)	8.08 (0.71)	8.08 (0.69)	8.13 (0.72)
Median	8.00	8.00	8.00
Min : Max	4.5 : 10.2	5.9 : 10.4	6.7 : 10.3
Week 30			
Number	443	446	221
Mean (SD)	6.50 (0.75)	6.81 (0.76)	7.31 (0.87)
Median	6.30	6.70	7.20
Min : Max	4.9 : 9.6	4.6 : 10.7	5.2 : 11.0
Change from baseline to Week 30			
Number	467	464	233
LS Mean (SE)[a]	-1.63 (0.038)	-1.34 (0.039)	-0.85 (0.052)
LS mean difference (SE) vs insulin glargine[a]	-0.29 (0.048)	-	-
95% CI	(-0.384 to -0.194)	-	-
p-value	<0.0001	-	-
LS mean difference (SE) vs lixisenatide[a]	-0.78 (0.059)	-	-
95% CI	(-0.898 to -0.665)	-	-
p-value	<0.0001	-	-

[a] Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination, insulin glargine alone, lixisenatide alone), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 4 (Week -1), randomization strata of second OAD use at screening (Yes, No), visit (Week 8, 12, 24, and 30), treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate.
Countries with fewer than 5 randomized patients were grouped with the country with the lowest number of randomized patients that is 5 or more.
The analysis included all scheduled measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.
Included are patients who have measurements at baseline and post-baseline.

Figure 7 Study EFC12404: Mean HbA1c (%) by visit during the study period - mITT population



S = Screening (Week -6), R = Run-in (Week -1), B = Baseline, LOCF = Last observation carried forward.
INS/LIXI = fixed ratio combination, INS = Insulin Glargine, LIXI = Lixisenatide
The plot included all scheduled measurements obtained during the study, including those obtained after IMP.

Secondary endpoints

Proportion of responders with HbA1c <7.0% or ≤6.5% at Week 30

The percentage of patients reaching HbA1c <7.0% was higher in the FRC group (73.7%) compared to both the insulin glargine group (59.4%) and the lixisenatide group (33.0%). The proportion difference was 14.3% (95%CI, 8.4% to 20.2%; p<0.0001) versus insulin glargine and 40.6% (95%CI [33.6% to 47.6%]; p<0.0001) versus lixisenatide.

The percentage of patients reaching HbA1c ≤6.5% was also higher in the FRC group (55.8%) compared to both the insulin glargine group (39.5%) and the lixisenatide group (19.3%). The proportion difference was 16.4% (95%CI, 10.1% to 22.6%; p<0.0001) versus insulin glargine and 36.4% (95%CI, 29.8% to 43.0%; p<0.0001) versus lixisenatide.

Prandial glucose control during a standardized meal test

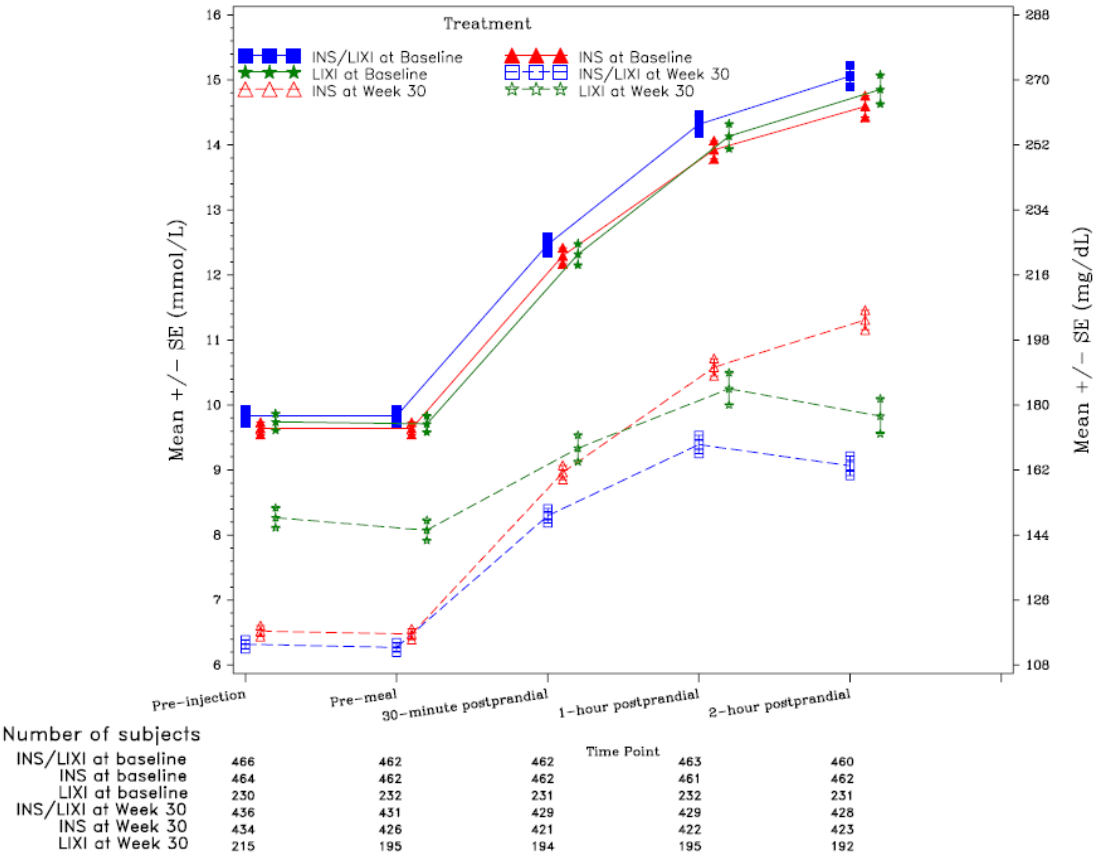
Treatment with the FRC significantly improved postprandial glycaemic control after a standardized liquid breakfast compared to insulin glargine, as shown by the results of change from baseline in 2-hour PPG excursions. The LS mean change was -2.31 mmol/L (-41.7 mg/dL) in the FRC group versus -0.2 mmol/L (-3.2 mg/dL) in the glargine group, with a LS mean treatment difference of -2.1 mmol/L (-38.4 mg/dL) (95%CI [-2.5 to -1.8]; p<0.0001, Test 1 in the testing order).

At Week 30, mean 2-hour PPG excursions were 2.8 mmol/L (50.7 mg/dL) for the FRC, 4.8 mmol/L (86.5 mg/dL) for insulin glargine, and 1.7 mmol/L (30.6 mg/dL) for lixisenatide.

There was also a substantially greater reduction from baseline in 2-hour PPG for the FRC as compared to both insulin glargine and lixisenatide (although these comparisons were not included in the statistical testing order). The LS mean change from baseline was -5.7 mmol/L (-102.4 mg/dL) for the FRC, -3.3 mmol/L (-59.6 mg/dL) for insulin glargine, and -4.6 mmol/L (-82.6 mg/dL) for lixisenatide.

At Week 30, mean pre-injection and pre-meal plasma glucose (PG) concentrations were similar between the FRC group and the insulin glargine group and higher in the lixisenatide group. Mean PG concentrations at all postprandial time points were lower in the FRC group than in the insulin glargine group and the lixisenatide group. In the FRC group and the lixisenatide group, the highest values were reached 1 hour after the start of the meal and then decreased while values continued to increase for up to 2 hours post-meal in the insulin glargine group (Figure 8).

Figure 8 Study EFC12404: Mean plasma glucose (mmol/L [mg/dL]) during a standardized meal test at baseline and Week 30 – mITT population



INS/LIXI = Fixed Ratio Combination, INS = Insulin Glargine, LIXI = Lixisenatide
The analysis included measurements collected during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.
Patients injecting IMP in the morning in the lixisenatide group and all patients in the combination or insulin glargine groups were included

Change in body weight from baseline to Week 30

Body weight decreased in the FRC and lixisenatide groups and increased in the insulin glargine group, with LS mean changes from baseline to Week 30 of -0.3, -2.3 and +1.1 kg for each group. There was a statistically significant difference in body weight change between the FRC and insulin glargine groups with a treatment difference of -1.4 kg (95% CI [-1.9 to -0.9]; p<0.0001, Test 2 in the testing order).

Change in FPG from baseline to Week 30

The reduction from baseline to Week 30 in FPG was significantly greater in the FRC group (-3.46 mmol/L) compared to the lixisenatide group (-1.50 mmol/L), treatment difference -1.96 mmol/L (95%CI [-2.25 to -1.68]; p<0.0001, Test 3 in the testing order). Starting from comparable baseline levels, the reduction in FPG was similar in the FRC (-3.46 mmol/L) and insulin glargine groups (-3.27 mmol/L).

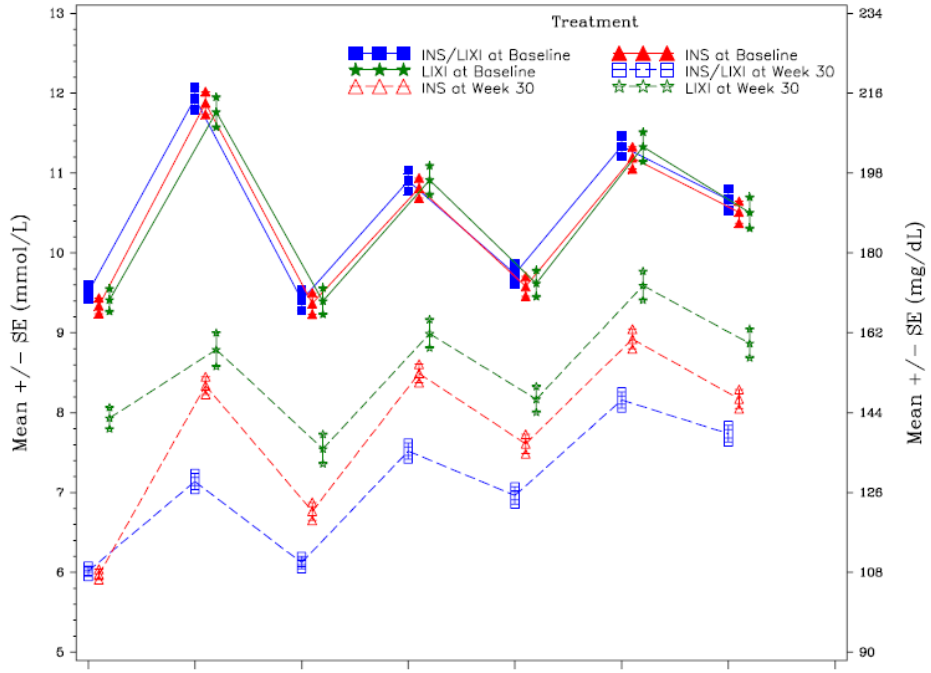
Mean FPG values at Week 30 were 6.32 mmol/L in the FRC and 6.53 mmol/L insulin glargine groups (113.9 mg/dL and 117.6 mg/dL). In the lixisenatide treated group mean FPG values at Week 30 were 8.27 mmol/L (148.9 mg/dL).

Change in the daily average of the 7-point SMPG from baseline to Week 30

Patients treated with the FRC had a statistically significantly greater reduction in average 7-point SMPG (-3.35 mmol/L [-60.36 mg/dL]) compared to patients in the lixisenatide group (-1.95 mmol/L [-35.11 mg/dL]; difference -1.40 mmol/L [-25.24 mg/dL], p<0.0001, Test 4 in the testing order) and compared to patients in the insulin glargine group (-2.66 mmol/L [-47.87 mg/dL]; difference -0.69 mmol/L [-12.49 mg/dL], p<0.0001, Test 7 in the testing order).

A graphic display of the 7-point SMPG profiles shows that values at all Week 30 time points were notably reduced from baseline and lower in the FRC group compared to the insulin glargine and lixisenatide groups. Exceptions were the similar pre-breakfast values for the FRC and insulin glargine groups, as observed for FPG values measured by the central laboratory (Figure 9). Importantly, the SMPG profiles at Week 30 demonstrate that improvement in glycaemic control was provided throughout the day in the FRC group.

Figure 9 Study EFC12404: Mean 7-point SMPG (mmol/L [mg/dL]) at baseline and Week 30 – mITT population



Number of subjects

INS/LIXI at baseline	459	452	447	454	448	445	418
INS at baseline	451	444	441	441	438	436	404
LIXI at baseline	226	226	221	224	223	222	206
INS/LIXI at Week 30	383	380	378	379	374	377	355
INS at Week 30	371	363	359	361	359	355	333
LIXI at Week 30	185	180	182	182	181	180	166

SMPG = Self-monitored plasma glucose. INS/LIXI = Fixed Ratio Combination, INS = Insulin Glargine, LIXI = Lixisenatide
The analysis included all scheduled measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.

Composite endpoints

- *Percent of patients reaching an HbA1c <7.0% with no body weight gain*

A statistically significantly higher proportion of patients reached this composite endpoint at Week 30 in the FRC group (43.2%) than in the insulin glargine group (25.1%); the treatment difference was 18.1% (95% CI [12.2% to 24.0%]; p<0.0001; Test 5 in the testing order). The proportion of patients reaching this composite endpoint was also markedly higher in the FRC group compared to the lixisenatide group (27.9%), and the treatment difference was 15.2% (95% CI [8.05%, 22.39%] excluding 0).

- *Percent of patients reaching HbA1c <7.0% with no body weight gain at Week 30 and with no documented symptomatic hypoglycemia during the study*

Significantly more patients in the FRC group reached the triple composite endpoint than did patients in the insulin glargine group (31.8% versus 18.9% respectively, with a treatment difference of 12.98% (95%CI [7.5% to 18.5%]; p<0.0001; Test 8 in the testing order). The proportion of patients reaching this triple composite endpoint was also numerically higher in the FRC group compared to the lixisenatide group (26.2%).

Insulin glargine dose

At Week 30, LS mean daily insulin doses were comparable in the FRC and glargine groups: 39.8 U in the FRC group and 40.3 U in the insulin glargine group (Test 9 in the testing order), corresponding to a mean daily insulin

dose adjusted by body weight of 0.45 U/kg in both groups. In both groups, the mean daily dose rose steadily and concordantly over the treatment period.

At the end of the treatment period, the proportion of patients taking doses ≥30 U was comparable between groups, 71.2% in the FRC group and 70.3% in the insulin glargine group. The maximum allowed dose of 60 U was taken by 15.6% of patients in the FRC group and 20.1% in the insulin glargine group. Two hundred and forty (51.2%) of patients were using Pen A, and 227 (48.4%) had switched and were using Pen B at the end of the treatment period.

Lixisenatide dose

In the FRC group, at Week 30, the mean daily dose of lixisenatide was 15.5 µg. The majority of patients (58.6%) were receiving ≥15 µg to ≤20 µg of lixisenatide at the end of the treatment period (Table 11).

Table 11 Study EFC12404: Number (%) of patients by final lixisenatide dose at the end of the treatment period – Fixed ratio combination group – Safety population

Final Lixisenatide Dose	Fixed Ratio Combination (N=469)
<10 µg	59 (12.6%)
≥10 µg to <15 µg	131 (27.9%)
≥15 µg to ≤20 µg	275 (58.6%)
>20 µg	2 (0.4%)

Note: Percentages are calculated using the number of safety patients as the denominator.

In the lixisenatide group, the majority of patients (88.8%) were receiving the recommended daily maintenance dose of 20 µg lixisenatide at the end of the treatment period.

Percent of patients receiving rescue therapy

Fewer patients received rescue therapy in the FRC group (3.6%) and the insulin glargine group (3.4%) (both groups capped at 60 U/day) as compared to the lixisenatide group (12.4%).

Hypoglycaemia

Comparable proportions of patients in the FRC (25.6%) and insulin glargine groups (23.6%) reported at least one event of documented symptomatic hypoglycaemia (PG ≤3.9 mmol/L [≤70 mg/dL]) as defined by the protocol. In the lixisenatide treated group, 6.4% of patients reported at least one event of symptomatic hypoglycaemia.

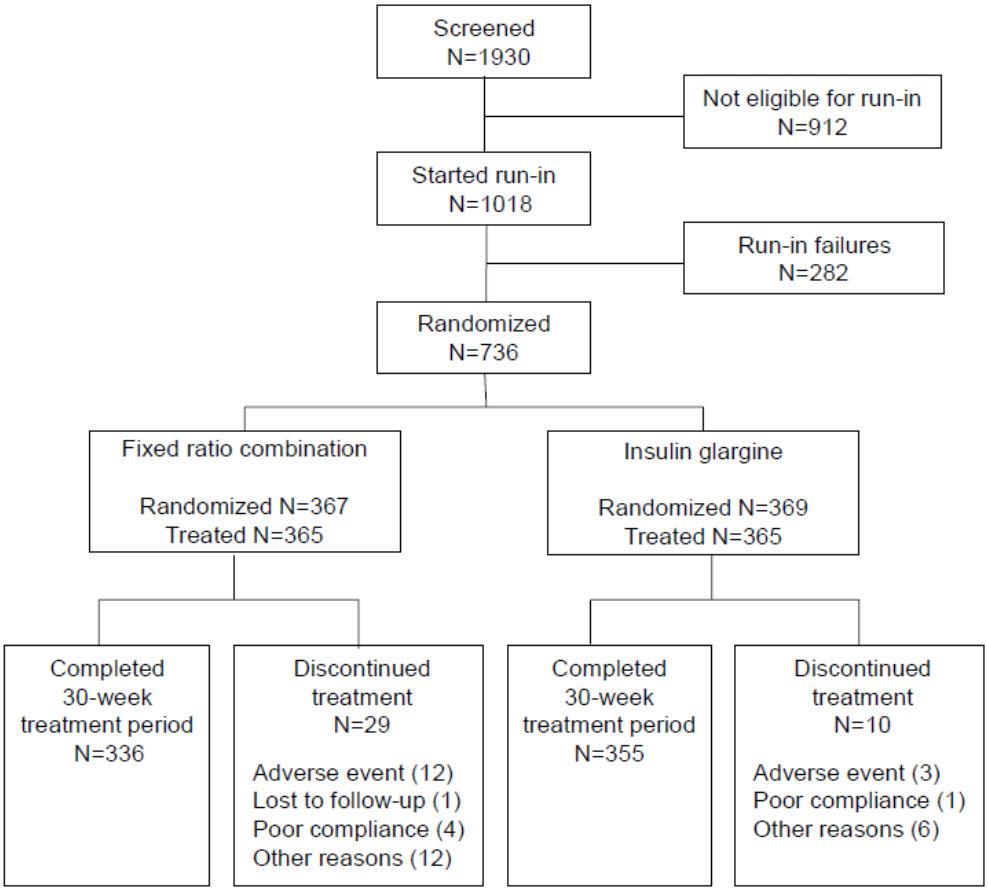
The corresponding number of events per patient-year was comparable between groups, 1.44 and 1.22 for the FRC and insulin glargine, respectively. One event of severe symptomatic hypoglycaemia was reported during the study and occurred in the insulin glargine group. In the lixisenatide treated group, the number of events per patient-year was 0.34.

When using the PG cut off of <3.3 mmol/L (60 mg/dL), the incidence of documented symptomatic hypoglycaemia with the FRC was 14.1%, with insulin glargine 10.7%, and with lixisenatide 2.6%, with corresponding numbers of events per-patient year of 0.25, 0.19, and 0.05, respectively.

Results - Study EFC12405

Participant flow

Figure 10 Study EFC12405: Patient disposition



The percentage of patients permanently discontinuing IMP during the open-label treatment period was higher in the FRC group (29 patients [7.9%]) than in the insulin glargine group (10 patients [2.7%]). The main reasons for IMP discontinuation were due to AEs (3.3% in the FRC group and 0.8% in the insulin glargine group) and other reasons (3.3% in the FRC group and 1.6% in the insulin glargine group).

Conduct of the study

There was one substantial amendment to the clinical study protocol dated 03 July 2014. Percentages of patients with major or critical efficacy deviations potentially impacting efficacy analyses were low.

Baseline data

Baseline demographics were well-balanced between treatment groups. The overall population was balanced by gender and was primarily Caucasian (91.7%) with 5.2% of Black patients and a mean age of 60 years. This was a population with a mean screening BMI of 31.3 kg/m^2 (BMI range 21-42) and with 58.6% of patients having a mean BMI ≥30 kg/m^2, indicating that the majority of the population was obese.

The majority of patients (92.0%) in the randomized population had a history of cerebrovascular events or cardiovascular risk factors, with hypertension being the most common (80.9% of patients) followed by dyslipidaemia (70.0% of patients). No major differences were observed between treatment groups.

The smoking and drinking habits were similar between treatment groups. Most patients (63.5%) did not smoke at screening and 51.1% of patients did not drink any alcohol in the last 12 months before screening.

A low percentage of patients (3.8%) had clinically significant physical examination findings at screening. No major differences were observed between treatment groups.

Screening and/or baseline characteristics related to diabetes were comparable in the 2 treatment groups. At screening, the mean duration of diabetes was 12.1 years with a mean HbA1c of 8.5% in both groups. At screening, the duration of basal insulin use was approximately 3 years in both groups, and the majority of all patients (64.4%) were receiving insulin glargine as their basal insulin. Patients receiving any basal insulin other than insulin glargine were switched to once daily insulin glargine at the start of run-in period. The overall mean daily dose of insulin glargine was approximately 29 U at the start of run-in and had increased to approximately 35 U at the time of randomization.

The percentage of patients using metformin at screening was comparable between groups with metformin used by 89.4% of all patients. The percentage of patients using 2 OADs at screening was 43.6% and 37.9% in the FRC and insulin glargine groups, respectively, with the most frequent combination being metformin plus a SU.

The inclusion criteria allowed patients pre-treated with basal insulin without metformin to be included in the trial. At randomization the proportion of patients using basal insulin alone was 11.4% (n=84/736).

Numbers analysed

The mITT population included 731 patients (99.3%) out of the 736 patients randomized; 5 patients (1 in the FRC group and 4 in the insulin glargine group) were excluded from the mITT population because they did not have any post-baseline efficacy data.

The safety population included 730 patients; 6 patients were randomized but not treated whereof 5 were not eligible and randomised by mistake, and 1 patient withdrew informed consent.

Table 12 Study EFC12405: Analysis populations

	Fixed Ratio Combination	Insulin Glargine	All
Randomized population	367 (100%)	369 (100%)	736 (100%)
Efficacy population			
Modified Intent-to-Treat (mITT)	366 (99.7%)	365 (98.9%)	731 (99.3%)
Safety population	365	365	730
PK population	356	0	356

Note:
The safety population patients are tabulated according to treatment actually received (as treated). For the efficacy population, patients are tabulated according to their randomized treatment.
There is no patient randomized in a group and taking another study treatment.
There is no patient having switched their treatment during the study.

Outcomes and estimation

Primary endpoint - Change in HbA1c from baseline to Week 30

The primary objective of the study was met as statistical superiority of the FRC over insulin glargine was demonstrated in change in HbA1c from baseline to Week 30.

A switch to insulin glargine from other basal insulins and/or dose titration during the run-in decreased mean HbA1c from 8.53% at screening to 8.08% at baseline (post run-in) in all patients.

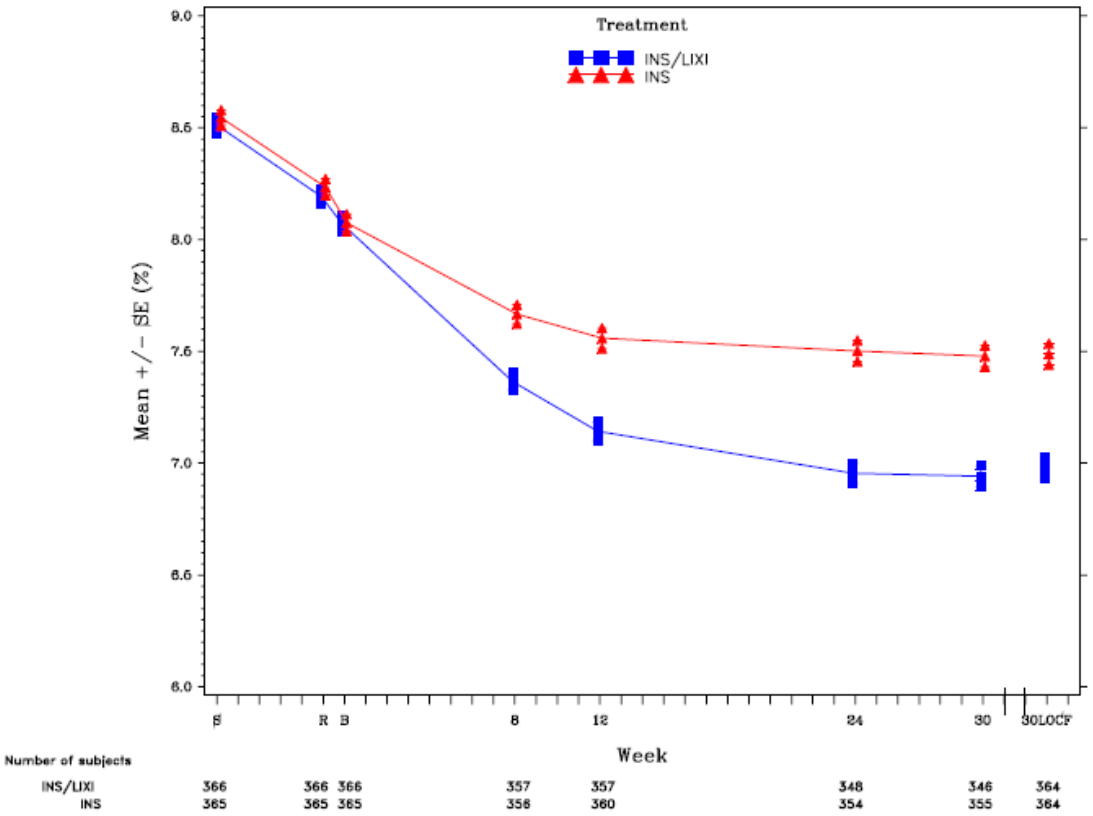
The changes in HbA1c from baseline to Week 30 were -1.13% for the FRC group and -0.62% for the insulin glargine group, reaching mean HbA1c levels of 6.94% and 7.48%, respectively (Table 13). The difference between the 2 treatment groups was -0.52% (95% CI: -0.633%, -0.397%). Statistical superiority of the FRC over insulin glargine was demonstrated (p<0.0001).

Table 13 Study EFC12405: Mean change in HbA1c (%) from baseline to Week 30 using MMRM - mITT population

HbA1c(%)	Fixed Ratio Combination (N=366)	Insulin Glargine (N=365)
Baseline		
Number	364	364
Mean (SD)	8.07 (0.68)	8.08 (0.73)
Median	8.00	8.00
Min : Max	6.6 : 10.2	5.9 : 10.0
Week 30		
Number	346	355
Mean (SD)	6.94 (0.87)	7.48 (0.91)
Median	6.80	7.40
Min : Max	5.0 : 9.8	5.6 : 11.2
Change from baseline to Week 30		
Number	364	364
LS Mean (SE)[a]	-1.13 (0.057)	-0.62 (0.055)
LS mean difference (SE) vs insulin glargine[a]	-0.52 (0.060)	-
95% CI	(-0.633 to -0.397)	-
p-value	<0.0001	-

[a] Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination and insulin glargine), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 5 (Week -1), randomization strata of metformin use at screening (Yes, No), visit (Week 8, 12, 24, and 30), treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as covariates.
Countries with fewer than 5 randomized patients were grouped with the country with the lowest number of randomized patients that is 5 or more.
The analysis included all scheduled measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.
Included are patients who have measurements at baseline and post-baseline.

Figure 11 Study EFC12405: Mean HbA1c (%) by visit - mITT population



S = Screening (Week -8), R = Run-in (Week -1), B = Baseline, LOCF = Last observation carried forward. INS/LIXI = Fixed Ratio Combination, INS = Insulin Glargine
Note: The plot included all scheduled measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue medication.

In the subgroup treated with basal insulin alone at randomisation, the change in HbA1c from baseline to Week 30 was -1.27% for the FRC group (n=41) and -0.42% for the insulin glargine group (n=43). The difference between the 2 treatment groups was -0.85% (95% CI: -1.197%, -0.499%).

Secondary endpoints

Percentage of patients reaching HbA1c ≤6.5% or <7% at Week 30

At Week 30, the percentage of patients reaching HbA1c <7% was markedly higher in the FRC group (54.9%) compared with the insulin glargine group (29.6%), proportion difference 25.5% (95%CI [18.9% to 32.1%]; p<0.0001).

This was also the case for the percentage of patients reaching HbA1c ≤6.5% (33.9% versus 14.2%), proportion difference 20.0% (95%CI [13.9% to 25.6 %]; p<0.0001).

In the subgroup treated with basal insulin alone at randomisation the responder rate (HbA1c <7%) was 56.1% in the FRC group (n=41) compared to 16.3% in the insulin glargine group (n=43), proportion difference 39.2% ((95%CI [20.7% to 57.6%]).

Prandial glucose control during a standardized meal test

Treatment with the FRC significantly improved postprandial glycaemic control after a standardized liquid breakfast in comparison to insulin glargine as shown by the results of change from baseline in 2-hour glucose

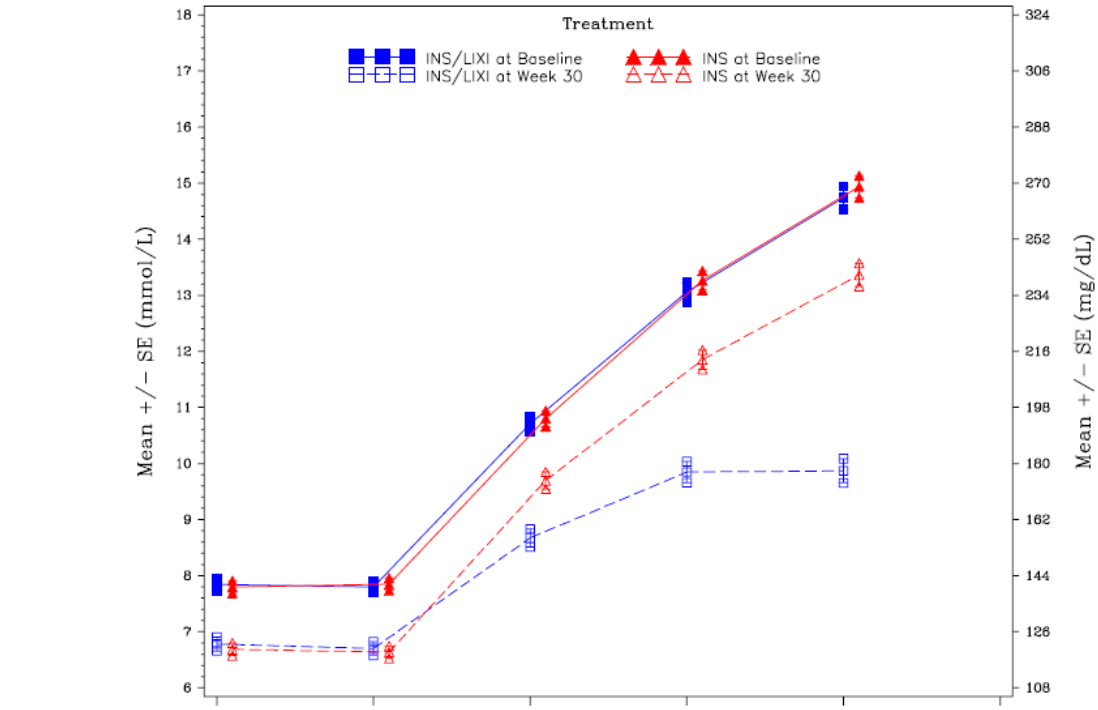
excursions. The LS mean change was -3.9 mmol/L (-70.2 mg/dL) in the FRC group versus -0.5 mmol/L (-8.4 mg/dL) in the glargine group with a LS mean treatment difference of -3.4 mmol/L (-61.8 mg/dL) (95%CI [-3.92 to -2.94]; p<0.0001; Test 1 in the testing order).

Mean 2-hour glucose excursions were 3.1 mmol/L (56.0 mg/dL) for the FRC and 6.7 mmol/L (120.8 mg/dL) for insulin glargine.

There was also a substantially greater reduction from baseline in 2-hour PPG for the FRC compared to insulin glargine (although this comparison was not included in the statistical testing order) (LS mean treatment difference: -3.3 mmol/L [-60.0 mg/dL], 95% CI: 3.89 mmol/L to 2.77 mmol/L [-70.07 mg/dL to -49.97 mg/dL]). Mean 2-hour PPG values at Week 30 were 9.9 mmol/L (178.6 mg/dL) for the FRC and 13.4 mmol/L (241.7 mg/dL) for insulin glargine.

At Week 30, mean PPG concentrations were markedly lower at all postprandial time points in the FRC group compared to the insulin glargine group (Figure 12). In the FRC group, a plateau was reached 1 hour after the start of the meal while values continued to increase for up to 2 hours in the insulin glargine group.

Figure 12 Study EFC12405: Mean plasma glucose (mmol/L [mg/dL]) during a standardized meal test at baseline and Week 30 – mITT population



INS/LIXI = Fixed Ratio Combination, INS = Insulin Glargine
The analysis included measurements collected during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.

Change in body weight from baseline to Week 30

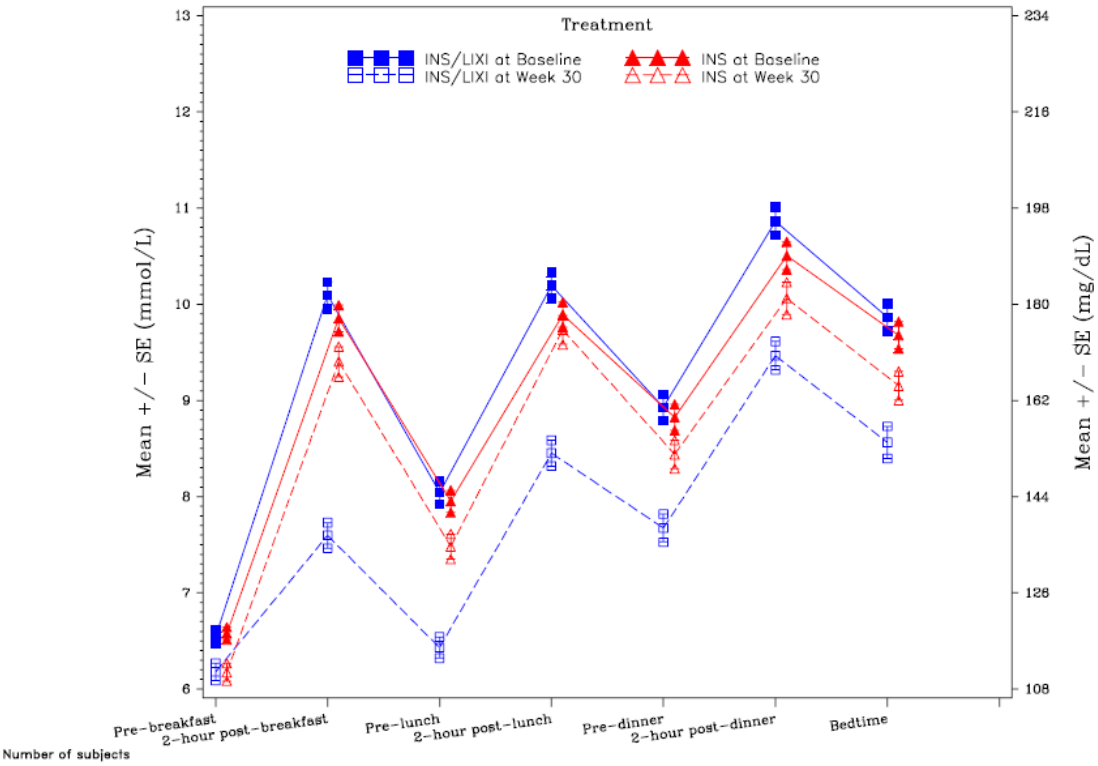
Mean body weight decreased in the FRC group by 0.67 kg and increased in the insulin glargine group by 0.70 kg. The LS mean treatment difference (-1.37 kg) between the two groups was statistically significant (95% CI [-1.808 to -0.930]; p<0.0001; Test 2 in the testing order).

Change in the daily average of the 7-point SMPG from baseline to Week 30

Patients treated with the FRC had a statistically significantly greater reduction in average 7-point SMPG (-1.50 mmol/L [-27.05 mg/dL]) compared to patients treated with insulin glargine (-0.60 mmol/L [-10.88 mg/dL]). The LS mean difference between the treatment groups was -0.90 mmol/L (-16.16 mg/dL) (p<0.0001; Test 3 in the testing order).

Figure 13 presents a graphic display of the 7-point SMPG profiles. Post-breakfast SMPG values at Week 30 time points had a clear reduction from baseline in the FRC treatment group. Values at all Week 30 time points but one were lower in the FRC group compared to the insulin glargine group. The one exception was observed pre-breakfast, when values were similar in the 2 groups, (as seen for FPG values measured by the central laboratory), which reflects the same titration to fasting SMPG target applied in both groups.

Figure 13 Study EFC12405: Mean 7-point SMPG (mmol/L [mg/dL]) at baseline and Week 30 – mITT population



SMPG = Self-monitored plasma glucose, INS/LIXI = Fixed Ratio Combination, INS = Insulin Glargine
The analysis included all scheduled measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.

Composite endpoints

- *Percent of patients reaching an HbA1c <7.0% with no body weight gain*

A significantly higher percentage of patients reached the composite endpoint in the FRC group (34.2%) compared to the insulin glargine group (13.4%), with a treatment difference of 20.8% (95%CI [15.0% to 26.7%]; p<0.0001; Test 4 in the testing order).

- *Percent of patients reaching HbA1c <7.0% with no body weight gain at Week 30 and with no documented symptomatic hypoglycaemia during the study*

Notably, more than twice as many patients in the FRC group (19.9%) reached the triple composite endpoint as compared to patients in the insulin glargine group (9.0%). The treatment difference was 10.94% (95% CI [5.93% to 15.96%]; Test 6 in the testing order). Inferential statistics were exploratory on this endpoint because the preceding test in the hierarchical testing order (change from baseline in dose of insulin) was not significant.

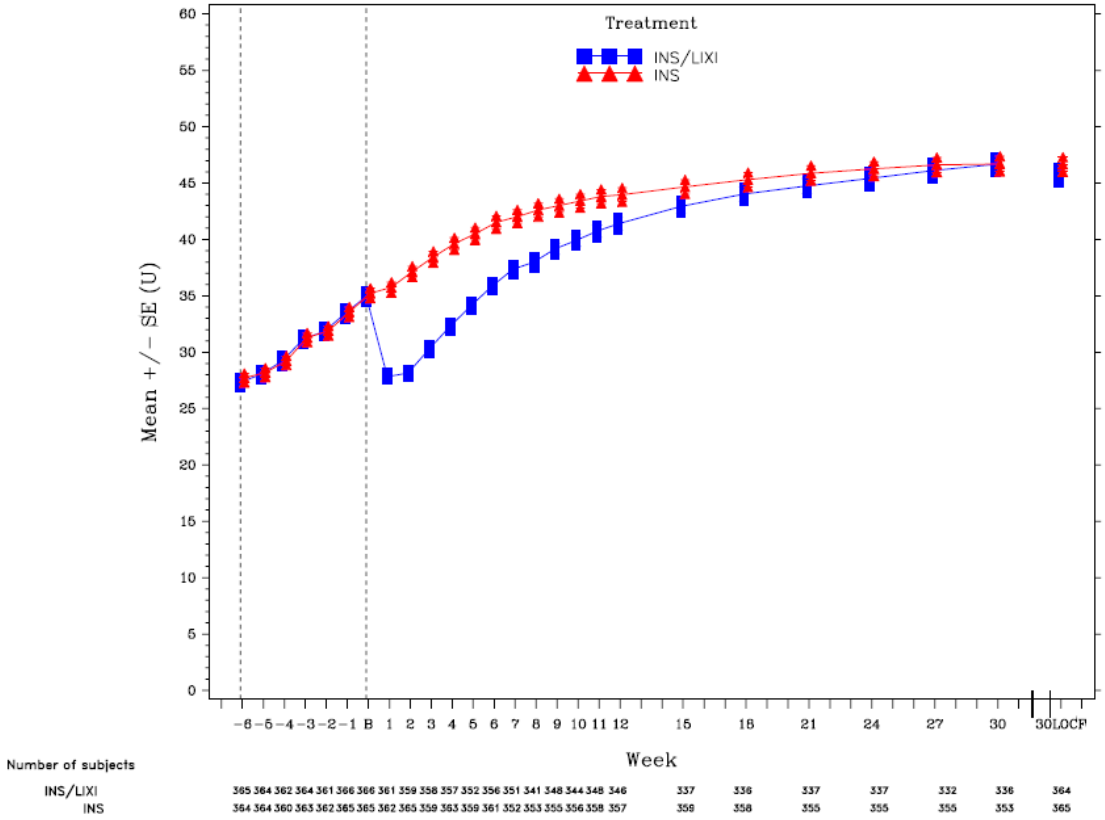
Insulin glargine dose

A comparable increase from baseline in the LS mean daily dose of insulin glargine was observed in both treatment groups (10.6 U in the FRC group and 10.9 U in the insulin glargine group) with an equivalent mean daily dose at Week 30 of approximately 47 U. Mean daily insulin dose adjusted by body weight was 0.54 U/kg in both groups.

As specified by the protocol and in order to comply with the recommended lixisenatide starting dose of 10 µg/day, investigators were to initiate treatment in the FRC group with a dose of either 20 U/10 µg with Pen A or 30 U/10 µg with Pen B, depending on the patient's previous daily basal insulin dose. This was reflected in a transient drop from baseline in the mean daily insulin glargine dose, followed by a steady rise (Figure 14). Beginning at Week 20, the mean daily dose began to plateau in both groups.

Because this endpoint was not statistically significant (Test 5 in the testing order), further testing was not performed on the other endpoints pre-specified in the hierarchical testing order.

Figure 14 Study EFC12405: Mean daily insulin glargine dose (U) by visit – mITT population



Week -6 = First Week of run-in, B=Baseline, LOCF = Last observation carried forward, INS/LIXI = Fixed Ratio Combination, INS = Insulin Glargine
The analysis included scheduled measurements obtained up to the date of last injection of IMP, including those obtained after introduction of rescue therapy.

At the end of the treatment period, the largest proportion of patients in any one dose-range were those taking >40 U to ≤60 U of insulin glargine, 60.8% in the FRC group and 64.7% in the insulin glargine group. The maximum allowed dose of 60 U was taken by comparable proportions of patients in the FRC (27.1%) and insulin glargine (30.7%) groups. One hundred (27.4%) of patients were using Pen A and 264 (72.3%) were using Pen B at the end of the treatment period.

Lixisenatide dose

In the FRC group, the mean daily dose at Week 30 was 16.9 µg. The majority of patients (68.8%) were receiving ≥15 µg to ≤20 µg of lixisenatide at the end of the treatment period.

Fasting plasma glucose

Starting from comparable baseline levels, the reduction in FPG was similar in the FRC and insulin glargine groups. The mean FPGs at Week 30 were 6.78 mmol/L and 6.69 mmol/L (122.1 mg/dL and 120.5 mg/dL).

Percent of patients receiving rescue therapy

The percentage of patients requiring rescue therapy was low in both groups and was lower for those receiving the FRC (2.7%) as compared to those receiving insulin glargine (6.0%) (dose capped at 60 U in both groups).

Hypoglycaemia

Comparable proportions of patients in each group reported at least one event of documented symptomatic hypoglycaemia (PG ≤3.9 mmol/L [≤70 mg/dL]): 40.0% and 42.5% in the FRC and insulin glargine groups, respectively. The number of events per patient-year was lower in the FRC group compared to the insulin glargine group (3.03 versus 4.22). There were 4 patients with severe symptomatic hypoglycaemia in the FRC group and 1 patient in the glargine group. Of these, 3 patients in the FRC group had alternative factors that may have contributed to the episodes of severe hypoglycaemia, including dementia, unusual amount of physical activity, and lack of food intake prior to the event.

When using the PG cut-off of <3.3 mmol/L (60 mg/dL), the incidence of documented symptomatic hypoglycaemia with the FRC was 24.4% and with insulin glargine 22.7%, with the corresponding number of events per-patient year of 0.44 and 0.40, respectively.

Summary of main efficacy results

The following tables summarise the efficacy results from the main 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 14 Summary of efficacy for trial EFC12404

Title: A randomized, 30 week, active-controlled, open-label, 3-treatment arm, parallel-group multicenter study comparing the efficacy and safety of insulin glargine/lixisenatide fixed ratio combination to insulin glargine alone and to lixisenatide alone on top of metformin in patients with Type 2 diabetes mellitus (T2DM)		
Study identifier	Study EFC12404	
Design	This was an open-label, 2:2:1 randomized, active-controlled, 3-group, 30-week treatment duration, parallel group multinational and multicenter study. Randomization was stratified by values of HbA1c at Visit 4 (Week -1) (<8%, ≥8%) and second oral anti-diabetic (OAD) use at screening (yes, no).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	30 weeks 4 weeks not applicable
Hypothesis	Superiority of FRC vs lixisenatide Non-inferiority of FRC vs insulin glargine	
Treatments groups	FRC (insulin glargine/lixisenatide)	469 subjects
	Insulin glargine	467 subjects
	Lixisenatide	234 subjects

Endpoints and definitions	Primary endpoint	Change in HbA1c (%) from baseline	The primary efficacy endpoint was change in HbA1c from baseline to Week 30.
	Secondary endpoints	2-hour PPG excursion	Change in 2-hour PPG and plasma glucose excursion during a standardized meal test from baseline to Week 30
		Body weight	Change in body weight from baseline to Week 30
		FPG	Change in fasting plasma glucose from baseline to Week 30
		7-point SMPG	Change in 7-point SMPG profiles from baseline to Week 30
		HbA1c <7% with no body weight gain	Percentage of patients reaching HbA1c <7% with no body weight gain at Week 30
		HbA1c <7% with no body weight gain and no hypo-glycaemia	Percentage of patients reaching HbA1c <7% with no body weight gain at Week 30 and with no documented symptomatic hypoglycaemia
		Insulin glargine dose	Average insulin glargine dose at Week 30

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat – 30 weeks from baseline			
Descriptive statistics and estimate variability	Treatment group	FRC	Insulin glargine	Lixisenatide
	Number of subject	467	466	233
	Change in HbA1c (%)	-1.63	-1.34	-0.85
	SE	0.038	0.039	0.052
	2-hour PPG excursion (mmol/L)	-2.31	-0.18	-3-23
	SE	0.154	0.157	0.216
	Body weight (kg)	-0.29	1.11	-2.30
	SE	0.182	0.183	0.256

	FPG (mmol/L)	-3.46	-3.27	-1.50
	SE	0.090	0.091	0.124
	7-point SMPG (mmol/L)	-3.35	-2.66	-1.95
	SE	0.081	0.084	0.111
	HbA1c <7% with no body weight gain (%)	43.2	25.1	27.9
	HbA1c <7% with no body weight gain and no hypoglycaemia (%)	31.8	18.9	26.2
	Insulin glargine dose (U)	39.77	40.46	NA
	SE	0.699	0.701	NA

Effect estimate per comparison	Primary endpoints		
	Change in HbA1c (%) from baseline Non-inferiority (superiority also confirmed)	Comparison groups	FRC - insulin glargine
		LS mean difference	-0.29
		95% CI	-0.384 to -0.194
		P-value	<0.0001
	Change in HbA1c (%) from baseline Superiority	Comparison groups	FRC – lixisenatide
		LS mean difference	-0.78 %
		95% CI	-0.898 to -0.665
		P-value	<0.0001
	Secondary endpoints		
	2-hour PPG excursion	Comparison groups	FRC - insulin glargine
		LS mean difference	-2.13 mmol/L
		95% CI	-2.498 to -1.770
		P-value	<0.0001
	Body weight	Comparison groups	FRC - insulin glargine
		LS mean difference	-1.40 kg
		95% CI	-1.891 to -0.910
		P-value	<0.0001
	FPG	Comparison groups	FRC – lixisenatide
		LS mean difference	-1.96 mmol/L

		95% CI	-2.246 to -1.682
		P-value	<0.0001
	7-point SMPG	Comparison groups	FRC – lixisenatide
		LS mean difference	-1.40 mmol/L
		95% CI	-1.645 to -1.158
		P-value	<0.0001
	HbA1c <7% with no body weight gain	Comparison groups	FRC - insulin glargine
		Proportion difference	18.08 %
		95% CI	12.15% to 24.01%
		P-value	<0.0001
	7-point SMPG	Comparison groups	FRC - insulin glargine
		LS mean difference	-0.69
		95% CI	-0.892 to -0.495
		P-value	<0.0001
	HbA1c <7% with no body weight gain and no hypo-glycaemia	Comparison groups	FRC - insulin glargine
		Proportion difference	12.98 %
		95% CI	7.50% to 18.45%
		P-value	<0.0001
	Insulin glargine dose	Comparison groups	FRC - insulin glargine
		LS mean difference	-0.69
		95% CI	-2.632 to 1.252
		P-value	0.4857
	FPG[a]	Comparison groups	FRC - insulin glargine
		LS mean difference	-0.19
		95% CI	-0.420 to 0.038
		P-value	0.1017
Notes	[a] per step-down procedure, analyses considered exploratory		

Table 15 Summary of efficacy for trial EFC12405

Title: A randomized, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group, multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination to insulin glargine with or without metformin in patients with Type 2 diabetes mellitus (T2DM)			
Study identifier	Study EFC12405		
Design	This was an open-label, 1:1 randomized, active-controlled, 2-group, 30-week treatment duration, parallel-group, multinational, and multicenter study. The randomization was stratified by HbA1c values at Visit 5 (Week -1) (<8%, ≥8%) and metformin use at screening (yes, no).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	30 weeks 6 weeks not applicable	
Hypothesis	Superiority of FRC vs insulin glargine		
Treatments groups	FRC (insulin glargine/lixisenatide)		367 subjects
	Insulin glargine		369 subjects
Endpoints and definitions	Primary endpoint	Change in HbA1c (%) from baseline	The primary efficacy endpoint was change in HbA1c from baseline to Week 30.
	Secondary endpoints	2-hour PPG excursion	Change in 2-hour blood glucose excursion during a standardized meal test from baseline to Week 30
		Body weight	Change in body weight from baseline to Week 30
		7-point SMPG	Change in 7-point SMPG profiles from baseline to Week 30
		HbA1c <7% with no body weight gain	Percentage of patients reaching HbA1c <7% with no body weight gain at Week 30
		Insulin glargine dose	Change in daily dose of insulin glargine from baseline to Week 30
		HbA1c <7% with no body weight gain and no	Percentage of patients reaching HbA1c <7% with no body weight gain at Week 30 and with no documented symptomatic hypoglycaemia

		hypo-glycaemia FPG	 Change in FPG from baseline to Week 30
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat – 30 weeks from baseline		

Descriptive statistics and estimate variability	Treatment group	FRC	Insulin glargine
	Number of subject	366	365
	HbA1c (%)	-1.13	-0.62
	SE	0.057	0.055
	2-hour PPG excursion (mmol/L)	-3.90	-0.47
	SE	0.285	0.274
	Body weight (kg)	-0.67	0.70
	SE	0.181	0.178
	7-point SMPG (mmol/L)	-1.50	-0.60
	SE	0.137	0.130
	HbA1c <7% with no body weight gain (%)	34.2	13.4
	Insulin glargine dose (U)	10.64	10.89
	SE	0.601	0.587
	HbA1c <7% with no body weight gain and no hypoglycaemia (%)	19.9	9.0
	FPG (mmol/L)	-0.35	-0.46
	SE	0.142	0.138

Effect estimate per comparison	Primary endpoint Change in HbA1c (%) from baseline	Comparison groups	FRC - insulin glargine
		LS mean difference	-0.52
		95% CI	-0.633 to -0.397
		P-value	<0.0001
	Secondary endpoints		
	2-hour PPG excursion	Comparison groups	FRC - insulin glargine
		LS mean difference	-3.43

		95% CI	-3.925 to -2.939
		P-value	<0.0001
	Body weight	Comparison groups	FRC - insulin glargine
		LS mean difference	-1.37
		95% CI	-1.808 to -0.930
		P-value	<0.0001
	7-point SMPG	Comparison groups	FRC - insulin glargine
		LS mean difference	-0.90
		95% CI	-1.154 to -0.640
		P-value	<0.0001
	HbA1c <7% with no body weight gain	Comparison groups	FRC - insulin glargine
		Proportion difference	20.82%
		95% CI	14.98% to 26.66%
		P-value	<0.0001
	Insulin glargine dose	Comparison groups	FRC - insulin glargine
		LS mean difference	-0.26
		95% CI	-1.762 to 1.246
		P-value	0.7362
	HbA1c <7% with no body weight gain and no hypoglycaemia[a]	Comparison groups	FRC - insulin glargine
		Proportion difference	10.94%
		95% CI	5.93% to 15.96%
		P-value	<0.0001
	FPG[a]	Comparison groups	FRC - insulin glargine
		LS mean difference	0.11
		95% CI	-0.207 to 0.428
		P-value	0.4951
Notes	[a] per step-down procedure, analyses considered exploratory		

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	241/995	32/995	2/995
Non Controlled trials	NA	NA	NA

Although the conclusion is based on a limited number of patients, there is no indication of a difference in benefit risk balance for the FRC when used in patients ≥75 years compared to younger patients. This is further supported by data from the lixisenatide file.

No dedicated studies in special populations were performed. This is acceptable considering that both components have been well characterised with regards to renal and hepatic impairment.

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

A pre-specified meta-analysis of change from baseline to Week 30 in HbA1c using pooled data from the 2 pivotal Phase 3 studies was performed by subgroup. Change from baseline was highly consistent across baseline categories including race, ethnicity, gender, age, baseline BMI, and baseline HbA1c (Table 16).

Patients that were ≥65 years of age had a treatment difference between the FRC and insulin glargine of -0.49 compared to a treatment difference of - 0.29 for patients <50 years of age and -0.35 for patients ≥50 and <65 years of age.

In patients ≥65 years, the greater reduction in HbA1c in the FRC group as compared to the insulin glargine group was not accompanied by an increased risk of hypoglycaemia in either the FRC or insulin glargine groups.

Change from baseline by age was consistent across all age categories in the meta-analysis as well as in EFC12405 (insulin-pretreated population). In EFC12404 (insulin-naïve population), in patients <50 years of age (n=85), the difference in HbA1c change from baseline between the FRC group and the insulin glargine group was -0.06% and the corresponding 95% CI included zero. In older patients, the differences were -0.32% (≥50 to <65 years, n=250) and -0.40% in the elderly (≥65 years, n=132) and the corresponding 95% CIs excluded zero.

Change from baseline by BMI was consistent across the two categories (<30 and ≥30) in the meta-analysis for the FRC. The treatment difference was however slightly higher for patients with BMI <30 compared to patients with BMI ≥30 (-0.46 and -0.33, respectively).

Table 16 Meta-analysis of change in HbA1c (%) from baseline to Week 30 by baseline factors using pooled data from the pivotal Phase 3 studies - mITT population

	Fixed Ratio Combination (N=834)				Insulin Glargine (N=831)	
			Compared to Insulin Glargine			
	N	LS Mean (SE)[a]	Difference in LS Mean (SE)[b]	95% CI[b]	N	LS Mean (SE)[a]
Race						
Caucasian/White	750	-1.48 (0.033)	-0.37 (0.040)	(-0.447 to -0.291)	751	-1.12 (0.033)
Black	50	-1.36 (0.117)	-0.51 (0.149)	(-0.802 to -0.218)	54	-0.83 (0.110)
Asian/Oriental	20	-1.36 (0.189)	-0.38 (0.273)	(-0.917 to 0.154)	15	-1.01 (0.206)
Other	11				8	-1.13 (0.273)
Ethnicity						
Hispanic	149	-1.40 (0.076)	-0.37 (0.088)	(-0.545 to -0.198)	151	-1.04 (0.074)
Non Hispanic	682	-1.48 (0.034)	-0.38 (0.042)	(-0.458 to -0.295)	677	-1.11 (0.034)
Age						
<50	135	-1.39 (0.068)	-0.29 (0.095)	(-0.471 to -0.100)	122	-1.12 (0.071)
>=50 to <65	454	-1.47 (0.041)	-0.35 (0.050)	(-0.448 to -0.250)	474	-1.13 (0.039)
>=65	242	-1.47 (0.052)	-0.49 (0.071)	(-0.629 to -0.351)	232	-0.95 (0.053)
Gender						
Male	386	-1.45 (0.042)	-0.34 (0.054)	(-0.446 to -0.233)	410	-1.11 (0.041)
Female	445	-1.46 (0.041)	-0.41 (0.052)	(-0.516 to -0.312)	418	-1.05 (0.042)
Baseline BMI (kg/m^2)						
<30	328	-1.47 (0.046)	-0.46 (0.060)	(-0.574 to -0.339)	334	-1.02 (0.046)
>=30	503	-1.45 (0.038)	-0.33 (0.048)	(-0.421 to -0.231)	494	-1.12 (0.039)
Baseline HbA1c (%)						
<8.0	387	-1.41 (0.049)	-0.37 (0.055)	(-0.480 to -0.264)	386	-1.04 (0.049)
>=8.0	444	-1.50 (0.046)	-0.38 (0.052)	(-0.482 to -0.279)	442	-1.14 (0.046)
Creatinine clearance categories at screening						
>= 30 -<60 (moderate decrease in GFR)	22	-1.08 (0.172)	-0.59 (0.285)	(-1.153 to -0.036)	12	-0.55 (0.228)
>= 60 -<90 (mild decrease in GFR)	219	-1.47 (0.055)	-0.40 (0.072)	(-0.544 to -0.262)	243	-1.07 (0.053)
>= 90 (normal)	586	-1.49 (0.036)	-0.37 (0.045)	(-0.460 to -0.284)	568	-1.11 (0.037)

BMI = body mass index.
[a] Weighted average of LS means of subgroup analysis from the individual studies with the inverse of variance as the weight.
[b] A fixed-effect meta-analysis method with the inverse of variance as the weight.
LS Mean and difference in LS Mean were provided for categories where at least one study had >= 5 patients in each treatment group.
The analysis included all scheduled measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.

Supportive study

Study ACT12374 (Phase 2 proof-of-concept study)

Study ACT12374 was a 1:1 randomized, 24-week, open-label, 2-arm, parallel-group, multicenter study comparing the efficacy and safety of the FRC versus insulin glargine in combination with metformin. Randomization (N=323) was stratified by screening HbA1c value (<8%, ≥8%) and screening body mass index (BMI) (<30 kg/m^2, ≥30 kg/m^2). The study was comprised of an up to 2-week screening period and a 24-week treatment period.

Major inclusion criteria were a diagnosis of T2DM for at least 1 year, treatment with metformin at a stable dose of at least 1.5 g/day for at least 3 months prior to screening, no use of insulin within the previous 6 months, screening HbA1c ≥7.0% or ≤10.0%, and screening FPG ≤13.9 mmol/L (≤250 mg/dL).

The fixed-ratio (2 U of insulin glargine/1 µg of lixisenatide) allowed daily insulin glargine doses ranging from 10 to 60 U and concomitant administration of between 5 µg and 30 µg lixisenatide. Both treatments were administered QD in the morning within 1 hour before breakfast. If a 60 U/30 µg dose was not sufficient to maintain FPG or HbA1c levels below thresholds values predefined for rescue therapy, the dose was to be kept at 60 U/30 µg and a rescue therapy was to be initiated. In the insulin glargine group there was no cap on the dose.

Results

The percentage of patients completing the 24-week treatment period was high in both treatment groups, 93.2% and 98.1%, for the FRC and insulin glargine groups, respectively.

The duration of diabetes, duration of metformin use, and average daily metformin dose at baseline were comparable between treatment groups. Overall, the median duration of diabetes was 5.4 years. Glycaemic parameters at baseline were generally similar in the 2 treatment groups with comparable mean (standard deviation [SD]) baseline values for HbA1c, 8.05% (0.80%) for the FRC and 8.01% (0.80%) for insulin glargine.

The FRC was non-inferior to insulin glargine. Statistical superiority of the FRC over insulin glargine was then tested and also demonstrated. The LS mean changes from baseline (standard error [SE]) to Week 24 were -1.82% (0.058%) for the FRC and -1.64% (0.057%) for insulin glargine, reaching mean (SD) HbA1c levels of 6.31% (0.72%) and 6.47% (0.64%), respectively, with a LS mean treatment difference of -0.17% (p=0.0130). Mean HbA1c decreased steadily over time in both groups with the lowest value observed at the last measurement (Week 24).

After a standardized meal at Week 24, treatment with the FRC significantly improved PPG control in comparison to insulin glargine.

- The FRC provided a significantly greater LS mean reduction from baseline in 2-hour PPG values versus insulin glargine. The LS mean change from baseline was -7.5 mmol/L (-135.0 mg/dL) for the FRC versus -4.3 mmol/L (-77.9 mg/dL) for insulin glargine with a LS mean treatment difference of -3.2 mmol/L (-57.1 mg/dL); p<0.0001.
- The FRC provided a significantly greater LS mean reduction from baseline in 2-hour PPG excursions versus insulin glargine. The LS mean reduction from baseline was 3.9 mmol/L (70.4 mg/dL) for the FRC and 0.7 mmol/L (12.0 mg/dL) for insulin glargine with a LS mean treatment difference of -3.2 mmol/L (-58.4 mg/dL); p<0.0001.

A statistically significant difference was observed between treatment groups for mean change in body weight. At Week 24, the LS mean reduction in body weight was 0.97 kg for the FRC versus an increase of 0.48 kg for insulin glargine (LS mean treatment difference of -1.44 kg; p<0.0001).

The average daily insulin glargine doses increased in both treatment groups over the treatment period. The LS mean daily average insulin glargine doses were comparable at Week 24: 36.1 U for the FRC group and 39.3 U for the insulin glargine group. There were comparable reductions in mean change from baseline to Week 24 in FPG between treatment groups with a LS mean change of -3.4 mmol/L (-60.3 mg/dL) for the FRC and -3.5 mmol/L (-63.3 mg/dL) for insulin glargine.

Significantly more patients treated with the FRC reached the composite endpoint of HbA1c <7.0% with no weight gain at Week 24 than patients treated with insulin glargine, 56.4% versus 37.3% (treatment difference: 19.0%, 95% CI: 8.57% to 29.51%). Significantly more patients reached the triple composite endpoint of HbA1c <7.0% with no weight gain at Week 24 and no documented symptomatic hypoglycaemia (plasma glucose concentration ≤3.9 mmol/L [≤70 mg/dL]) compared to insulin glargine-treated patients, 46.3% versus 28.6% (treatment difference: 17.7%, 95% CI: 7.46% to 27.97%).

2.4.7. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the fixed-ratio combination in patients with T2DM was assessed in two pivotal phase 3 active-controlled, 30-week, open-label studies in patients with type 2 diabetes mellitus (T2DM); study EFC12404 and study EFC12405.

Study EFC12404 was designed to evaluate the contribution of the respective components insulin glargine and lixisenatide to the effect of the FRC. This study only included patients who were insulin naïve. Study EFC12405 evaluated the FRC in patients on basal insulin therapy, with insulin glargine as the active comparator. All patients included had to be treated with basal insulin for at least 6 months. Thus this study was designed to support the use in of the FRC in patients switching from basal insulin. The objectives as well as the primary and secondary endpoints were adequate. The inclusion and exclusion criteria were adequate to ensure that a population representative for the target population was included in the studies. The development program is considered adequate in order to support an application for a fixed combination, although it should be noted that both studies were of relatively short duration (30 weeks).

The open-label design used in both studies is accepted although a double-blind study is preferable, especially when the objective is non-inferiority (Study EFC12404). The randomisation was, in both studies stratified by value of HbA1c (<8%, ≥8%) during run-in and in study EFC12404 also second oral anti-diabetic drug (OAD) use at screening (yes, no) and in study EFC12405 metformin use at screening (yes, no). To be eligible for randomisation a patient had to have a value of HbA1c ≥7% and ≤10% at the end of the run-in period.

The Applicant has developed two pens in order to accommodate both the expected dose range for insulin glargine as well as the dose range for lixisenatide, thus to avoid exceeding the maximum dose of 20 µg lixisenatide. When a patient switches from Pen A to Pen B, without changing the insulin dose, this will lead to a decrease in the lixisenatide dose by a maximum of 7 µg (at an insulin dose of 40 U).

The Applicant has provided data supporting that the dose decrease in lixisenatide when patients transition from Pen A to Pen B does not have an adverse impact on glycaemic control.

A human factors study has been conducted in order to investigate whether the dosing concept is understandable for the intended users; this issue is further discussed in the safety and RMP sections.

The FRC was to be administered before breakfast in both studies. This is not entirely in line with the proposed SmPC, which states that the FRC may be given before any meal. In study EFC12404, the starting dose at randomisation was set according to the insulin glargine label (i.e. 10 U). With this starting dose, a lixisenatide dose of 5 µg will be administered, which is below the recommended starting dose for lixisenatide. However, data have been provided that show that an effect of lixisenatide is observed already at this dose (see section Pharmacodynamics). In study EFC12405, the patients entered the run-in with their previous insulin dose. This dose was then further titrated to achieve the target set for randomisation. The insulin glargine dose could be given at any time of the day. At randomisation, the starting dose was based on the lixisenatide component. Thus, depending on the patient's insulin dose at randomisation, either Pen A or Pen B was to be used in order to administer 10 µg of lixisenatide while providing an insulin dose as close as possible to the insulin dose reached during titration.

An adequate dose adjustment algorithm was in place, which was applied for both the FRC treated groups and those treated with insulin glargine in both studies. The maximum dose of FRC to be given was 60 U/20 µg. This dose was maintained also if rescue medication was introduced. In both studies the maximum allowed insulin

glargine dose in the comparator arm was capped at 60 U. This is from a methodological point of view considered acceptable in study EFC12404 where the combination was to be compared to each of its components respectively. In study EFC12405 where the primary objective was to demonstrate superiority FRC vs. insulin glargine, the comparison may seem less fair since insulin glargine may then be used at a suboptimal dose. Study EFC12405 can therefore not provide any answer regarding whether the FRC is per se a better treatment option than insulin glargine alone in a setting where insulin glargine is used without any limitations, i.e. when basal insulin therapy is optimized, at least not with regard to reaching and keeping HbA1c targets. This is however less of an issue concerning known negative effects of insulin treatment (e.g. impact on body weight and the risk of hypoglycaemia).

In study EFC12404, lixisenatide was given in accordance to label. The maintenance dose of 20 µg could be reduced if not tolerated.

Relevant criteria for when to start rescue medication were in place. For the lixisenatide group, the choice of rescue treatment was left at the Investigator's discretion, whereas for the FRC and insulin glargine treated groups, specific recommendations were given. This is acceptable considering that no other GLP-1 RA, DPP-4 inhibitor or basal insulin should be used as rescue medication in any of the 3 treatment groups.

In Study EFC12404 the non-inferiority margin was set to 0.3%, which is commonly accepted. For the superiority hypothesis a difference of 0.4% was assumed in both studies and hence, irrespective of comparison; FRC versus lixisenatide or FRC versus insulin glargine. With the non-inferiority margin 0.3% supposed to represent a non-clinically relevant difference, a difference >0.4% may have been more appropriate. With regard to study powering the assumption of a smaller difference as opposed to a bigger is however conservative.

In both Phase 3 pivotal studies the statistical methodology was similar although differed with respect to non-inferiority/superiority testing of the primary efficacy endpoint and the order of hierarchical testing for the key secondary endpoints. The principal features of the statistical analyses planned are overall acceptable. Analyses of the primary endpoint were based on a mixed-effect model with repeated measures (MMRM) under the missing at random framework. It is endorsed that several sensitivity analyses were planned and have also been performed. There was no PP population defined in any of the studies; foremost potentially an issue in study EFC12404 considering the non-inferiority objective. Analyses were performed with or without censoring of HbA1c measurements obtained after IMP discontinuation or introduction of rescue therapy with the latter being the primary approach.

In study EFC12404 a high percentage of randomised and treated patients completed the open-label study treatment period; 440/469 (93.8%) in the FRC arm, 440/467 (94.2%) in the insulin glargine arm and 205/233 (87.6%) in the lixisenatide arm. The proportion of patients who required rescue therapy was low and, at least in the FRC and insulin glargine treatment group also very similar; 3.6% (17/468) and 3.4% (16/466) respectively. In the lixisenatide arm 12.4% (29/233) required rescue therapy.

Also in study EFC12405 a high percentage of patients completed the open-label treatment period although slightly fewer in the FRC than in the insulin glargine arm; 91.6% (336/367) and 96.2% (355/369) respectively. The proportion of patients requiring rescue therapy was lower in the FRC arm than in the insulin glargine arm, 2.7% (10/366) and 6.0% (22/365).

The included population in the Phase 3 trials had a mean BMI of >30, indicating that they were obese. It is not clear whether this fixed ratio combination is also efficacious in a non-obese population (e.g. BMI<25). It is a fact that diabetic patients with low BMI are more likely to have beta cell destruction rather than insulin resistance as an underlying cause for their diabetes and therefore GLP-1 analogues are less suited to treat these patients.

Efficacy data and additional analyses

Study EFC12404

Baseline data are considered representative for a T2DM population failing on OAD treatment and that would benefit from insulin initiation. Notably the mean BMI was high (31.7). Only 3 % of subjects were older than 75 years. The mean metformin dose was 2250 mg, it is however noted that 8 subjects (0.7 %), evenly distributed between treatment groups, used a metformin dose <1500 mg daily. A comparable, low proportion of patients in the FRC and insulin glargine groups received rescue therapy (3.4% and 3.6%, respectively), whereas the proportion was higher in the lixisenatide group (12.4%).

The primary objective of the study was met as superiority for the FRC vs lixisenatide was shown as well as both noninferiority and superiority for the FRC vs insulin glargine. The change in HbA1c from baseline was 1.63 % in the FRC treated group. Notably, the treatment difference in change in HbA1c between FRC and insulin glargine was only about 0.3 %, which is of borderline clinical relevance, whereas the treatment difference between FRC and lixisenatide was about 0.8 %. Thus it appears that insulin glargine contributes the major part of the FRC effect. These data are in line with the outcome for the fixed combination insulin degludec/liraglutide, where the treatment difference between insulin degludec/liraglutide and insulin degludec was -0.47% and -0.64% between insulin degludec/liraglutide and liraglutide in a trial of 26 weeks duration (baseline HbA1c 8.3%).

Considering that few patients lacked data at Week 30 and also that all efficacy assessments were included, irrespective of requiring rescue therapy or treatment discontinuation, primary outcomes are considered statistically convincing. While the “all assessments approach”, which includes efficacy assessments when a patient was on rescue, may be conservative in the superiority setting it may not when the aim is non-inferiority. However, regarding the comparison versus insulin glargine, not only non-inferiority but also superiority was shown. While a PP population had been expected in study EFC12404 the lack thereof is acceptable; with data/information in hand a PP population is not considered to differ that much from the mITT population as to change the conclusion of non-inferiority, FRC vs. insulin glargine. All sensitivity analyses performed showed very similar outcomes compared to the primary analysis. Thus the data is considered robust.

When the change in HbA1c was plotted over time, the curves separated already after 8 weeks. For the FRC and for lixisenatide, it appears as if the maximal effect has been reached at six months whereas the curve for insulin glargine showed a continuous decrease throughout the study.

The effect of the three different treatments on PPG was studied during a standardized meal test. A greater change in mean 2-hour PPG excursions from baseline was observed for the FRC treated group (-2.31 mmol/L) compared to the insulin glargine treated group (-0.2 mmol/L). The treatment difference was statistically significant (-2.1 mmol/L, 95%CI, -2.5 to -1.8; p<0.0001). The corresponding change in mean 2-hour PPG excursion for lixisenatide was -3.23 mmol/L. Notably, the pre-meal PG was comparable and lower in the FRC and insulin glargine treated groups compared to the lixisenatide group. In the FRC and lixisenatide treated groups, the highest PPG was observed 1 hour after the meal, whereas PPG had not started to decline at 2 hours in the insulin glargine treated group.

The FPG at baseline was comparable in the three treatment groups. At week 30, the effect on FPG was comparable in the FRC and insulin glargine treated groups, and mean values were well within the target range (6.32 mmol/L and 6.53 mmol/L, respectively). For lixisenatide the FPG at week 30 was 8.27 mmol/L. This is in line with the differences observed for the pre-meal PG recorded in the standardized meal test. The treatment difference in change in FPG from baseline between the FRC and the lixisenatide treated groups was statistically significant.

There was a notable reduction in SMPG profiles with all three treatments compared to baseline. The average 7-point SMPG was statistically significantly lower in the FRC treated group (-3.4 mmol/L) compared to both the lixisenatide (-2.0 mmol/L) and insulin glargine (-2.7 mmol/L) treated groups. Compared to insulin glargine, the FRC treated group showed lower pre- and post-prandial values at all time points except for the pre-breakfast (FPG) value. This appears to be mainly driven by a lower PPG excursion after breakfast with FRC.

Thus the data on 2-hour PPG excursions, FPG and SMPG profiles are consistent and indicate that the insulin component mainly affects the FPG levels and the lixisenatide exerts its main effect on PPG levels.

Body weight remained stable in the FRC treated group (-0.3 kg) whereas body weight increased in the insulin glargine group (1.1 kg) and decreased in the lixisenatide group (-2.3 kg). The treatment difference between FRC and insulin glargine of -1.4 kg was statistically significant (95% CI [-1.9 to -0.9]; p<0.0001).

Although numerically higher in the FRC group, the proportion of patients reporting symptomatic hypoglycaemias were was rather low and comparable in the FRC (25.6 %) and insulin glargine (23.6 %) treated groups. As expected, the rate of hypoglycaemias was lowest in the lixisenatide group (6.4 %).

The proportion of patients achieving both either the target of < 7% and or ≤6.5% was higher in the FRC treated group (74 % and 56 %) compared to both insulin glargine (59 % and 40 %) and lixisenatide (33 % and 19 %). A statistically significantly higher proportion of patients reached the target "HbA1c < 7 % with no body weight gain" in the FRC group (43.2%) compared to the insulin glargine group (25.1%). The proportion was also higher in the FRC group compared to the lixisenatide group (27.9%). A higher proportion of patients in the FRC group (31.8%) reached the triple composite endpoint (HbA1c < 7%, no body weight gain and no documented symptomatic hypoglycaemias) compared to both the insulin glargine group (18.9%) and the lixisenatide group (26.2%). The treatment difference between FRC and insulin glargine was statistically significant.

There were no difference in insulin doses between the FRC and insulin treated groups at week 30. The mean daily dose rose concordantly over the treatment period. The distribution of patients across different dose levels was comparable. A slightly higher proportion of patients in the insulin glargine group (20.1 %) used 60 U at week 30 compared to the FRC group (15.6 %). For a further understanding of efficacy among patients using the maximum dose allowed (60U) the Applicant was asked to perform additional subgroup analyses based on the subgroups >40U to <60U and =60U respectively. The data show that in the proportion of patients reaching the maximum FRC dose of 60 dose steps, about 50 % reached the target with this dose. Thus the proportion of patients that could potentially benefit from a different therapy was low at 30 weeks.

It is noted that two patients in the insulin glargine treated group were using more than 60 U daily at the end of study.

The data on insulin doses is somewhat in contrast to the data for insulin degludec/liraglutide, where the insulin dose was lower (38 U) in the insulin degludec/liraglutide arm compared to the insulin degludec arm (53 U) at 26 weeks. It should be noted that the insulin degludec dose was not capped in that study.

The mean lixisenatide dose in the FRC group was 15.5 µg at week 30. The mean lixisenatide dose in the monotherapy group was not calculated, but 89 % of patients were receiving the recommended maintenance dose of 20 µg. Notably, two patients are reported to have used > 20 µg in the FRC treated group. This was due to incorrect use of Pen A.

Study EFC12405

Baseline data are considered representative for a T2DM population on insulin treatment. Notably the mean BMI was high (31.3). Thirty-nine patients (5.3 %) were older than 75 years. The mean insulin dose at screening was

29 U. The inclusion criteria stated that the insulin dose should be ≥20 U at randomisation. There were a total of 7 patients with an insulin dose <20 U at randomisation (5 patients in the FRC group and 2 in the insulin glargine group). Although the patients were not evenly distributed between groups, this discrepancy from the inclusion criterion is not considered to have an effect on the outcome as the deviation from the target in most cases was small and the number of patients low.

The study met its primary endpoint. The change in HbA1c from baseline in the FRC group was larger than the change in the insulin glargine group with a treatment difference of -0.52% (95% CI [-0.63% to -0.40%]; p< 0.0001). Based on the limited amount of missing data and the proportion of patients who discontinued the treatment period and/or study treatment the difference shown between treatments in favour of FRC is considered statistically convincing. The percentage of patients with HbA1c value at Week 30 was slightly less in the FRC than in the insulin glargine treatment arm; 94.5% (346/366) compared to 97.3% (355/365) respectively. Of the patients randomised, there were more patients in the FRC arm than in the insulin glargine arm who did not complete the open-label treatment period, 29/367 (7.9%) and 10/369 (2.7%) respectively. There was also more patients in the FRC group than in the control group that discontinued study treatment; 19/367 (5.2%) compared to 7/369 (1.9%). Despite these differences in treatment/study compliance pattern, they are numerically considered to be limited and as such not considered to be of any major concern regarding the primary conclusion.

The outcome in the subgroup of patients on basal insulin alone at randomisation was comparable to that of the overall population.

Again the data are in line with the outcome of a study of comparable design comparing insulin degludec/liraglutide with insulin degludec where the estimated treatment difference was -1.05 % (baseline HbA1c 8.7-8.8%).

When the change in HbA1c is plotted over time, the curves have separated already after 8 weeks. The effect of insulin glargine appears to have reached a plateau already at 12 weeks whereas HbA1c showed further decrease up to 24 weeks in the FRC treated groups. It appears as if the maximal effect has been reached at six months for both treatments.

One concern with the design of study EFC12405 was the capping of the insulin glargine dose at 60 U per day. However, at the end of the 30 week study period, the insulin dose did not differ between groups (mean dose about 47 U, 0.54 U/kg body weight). A slightly higher proportion of patients in the insulin glargine treated group (31%) was using the maximum dose allowed (60 U) than in the FRC treated group (27%). Taking the low proportion of patients needing rescue in both study arms (2.7% [10/366] for FRC and 6.0% [22/365] for insulin glargine), the capping of the insulin glargine dose appears not to have affected the outcome to a greater extent in this short-term study. In post hoc analyses performed, HbA1c responders (<=6.5%/<7%) was evaluated also by final insulin dose category. The outcomes across dose category subgroups were fairly consistent within each treatment arm respectively with the biggest difference between treatments (FRC, insulin glargine) seen in the highest dose category (>40U to ≤60U) including 60.8% (222/365) of the patients in the FRC arm and 64.7% (236/365) of the patients in insulin glargine arm respectively. For a further understanding of efficacy among patients using the maximum dose allowed (60U) the Applicant was asked to perform additional analyses based on the subgroups >40U to <60U and =60U respectively. Within each treatment arm the subgroups of subjects who had reached a final insulin dose of 60 U had the numerically lowest response rates (HbA1c <7%) when compared with the subgroups with lower final insulin doses. Given that the same pattern was seen in both treatment arms, additional support is seemingly offered that the capping of the insulin glargine dose in the control arm in Study EFC12405 appears not to have affected the outcome to a greater extent in this short-term study. The data also show that in the subgroup of patients reaching the maximum FRC dose of 60 dose steps,

43.4% (43/99) reached the target with this dose. Thus the proportion of patients that could potentially benefit from a different therapy was low at 30 weeks (approx. 15%; 56/365).

A similar reduction from baseline in FPG was observed in the two treatment groups, with a mean FPG within target for both groups (6.78 mmol/L and 6.69 mmol/L, respectively). Thus the dose titration was similarly efficient for both treatments. In this study the decrease in FPG was less pronounced than in study EFC12404, probably due to the titration of insulin in the screening phase. It also appears as if the contribution of the lixisenatide component to the decrease in FPG was small as there was no "insulin saving" effect with the FRC, i.e. the mean insulin dose was similar in both groups at week 30.

The mean daily dose of lixisenatide at 30 weeks was 16.9 µg. The majority of patients were using a dose ≥15 µg to ≤20 µg, thus very close to the recommended maintenance dose of lixisenatide when used as monotherapy.

As in study EFC12404, the effect on PPG excursions was investigated after a standardized meal. A decrease of -3.9 mmol/L in the mean 2-hour PPG excursions was observed for the FRC treated group compared to -0.5 mmol/L in the insulin glargine treated group. The treatment difference was statistically significant (-3.4 mmol/L, 95%CI [-3.92 to -2.94]; p<0.0001). The mean 2-hour PPG excursions were 3.1 mmol/L for the FRC and 6.7 mmol/L for insulin glargine. The pre-meal PG was comparable in the two treatment groups. While PPG was still increasing at two hours post-meal in the insulin glargine treated group, the PPG had reached a plateau at one hour post-meal in the FRC treated group. Thus these findings were consistent with those observed in study EFC12404.

These data are in accordance with the data on the SMPG where the reduction in average 7-point SMPG was greater in the FRC treated group (-1.50 mmol/L) compared to patients treated with insulin glargine (-0.60 mmol/L). The treatment difference between groups (-0.90 mmol/L) was statistically significant (p<0.0001). The FRC treated patients showed a less marked increase in post-breakfast PG which resulted in lower pre-lunch PG. The PPG excursions after lunch and dinner appear comparable between treatments, but due to the lower pre-lunch values in the FRC, all PG values remained lower than those observed in the insulin glargine treated group.

Mean body weight decreased slightly in the FRC treated group (-0.67 kg) while it increased in the insulin treated group (0.70 kg). The treatment difference of -1.37 kg was statistically significant (95% CI [-1.808 to -0.930]; p<0.0001).

The proportion of patients reporting symptomatic hypoglycaemias was comparable between the groups (40% with FRC and 43% with insulin glargine). Few episodes of severe symptomatic hypoglycaemia were reported (4 patients in the FRC group and 1 in the insulin glargine group).

In the responder analyses comparing the proportion of patients with HbA1c value ≤ 6.5% or <7% at Week 30 respectively, there were statistically significant differences between FRC and insulin glargine in the favour of the FRC. Patients without assessments at week 30 were treated as non-responders. A statistically significant higher proportion of patients treated with the FRC reached the composite endpoint of" HbA1c <7% with no body weight gain" (34.2%) compared to the insulin glargine treated group (13.4%). The proportion of patients who achieved the triple composite endpoint "HbA1c <7% without body weight gain and no documented symptomatic hypoglycaemia" was also higher in the FRC treated group (20%) than in the insulin glargine treated group (9%).

Special populations

Although the number of patients is limited, there is no indication of a difference in benefit risk balance for the FRC when used in patients ⩾75 years compared to younger patients. This is further supported by data from the lixisenatide file. The limited experience is adequately reflected in the SmPC.

No dedicated studies in special populations were performed. This is acceptable considering that both components have been well characterised with regards to renal and hepatic impairment.

Sub group analysis

A sub group analysis was performed on the pooled data from both studies. The effect of the FRC was comparable across all subgroups studies, except for subjects with GFR between 30 and 60. In this group a slightly lower decrease in HbA1c was observed, however the number of subjects was low. Notably, the difference in outcome in subjects with baseline HbA1c < 8% and >8% was small (-1.41% and -1.50%, respectively). The treatment difference compared to insulin glargine was also rather consistent across groups. It may be noted that the treatment difference increased slightly with age in favour of the FRC. The treatment difference was also slightly higher in females and in subjects with BMI <30 kg/m^2. Additional subgroup analysis for patients with BMI ≤25, BMI >25 and ≤30 showed that efficacy in terms of HbA1c reduction was maintained across the range of BMI.

Supportive data

Study ACT12374 was a 24-week, phase 2 study which included 323 insulin naïve patients and compared the FRC (maximum dose 60 U/30 µg) to insulin glargine. The insulin glargine dose was not capped in this study. The study met its primary objective to show that the FRC was non-inferior to insulin glargine with regards to change in HbA1c from baseline. Further testing demonstrated that the FRC was superior to insulin glargine. No difference was observed in change from baseline in FPG and at the end of the study, and insulin doses were comparable between groups. The data from this study are in line with those presented with the pivotal studies.

2.4.8. Conclusions on clinical efficacy

The FRC has been investigated in a clinical programme of adequate design. The FRC is provided in two different pens with two different ratios between insulin glargine and lixisenatide which may increase the risk for medication errors. Study EFC12404 provides relevant information on the contribution of the mono-components to the effect of the FRC. Insulin glargine primarily reduces HbA1c by decreasing the fasting plasma glucose whereas lixisenatide primarily reduces the post-prandial glucose excursion. The major contribution in HbA1c is due to insulin glargine as the treatment difference between the FRC and insulin glargine ranged from 0.3 % to 0.5 %, whereas the treatment difference between the FRC and lixisenatide was 0.8 %. With the FRC, the decrease in HbA1c was achieved without increase in body weight, and without an increase in the reporting of hypoglycaemia compared to patients on monotherapy with insulin glargine. There was no difference in insulin dose with the FRC compared to monotherapy with insulin glargine in any of the studies, thus there was no insulin "saving" effect with the FRC when the insulin dose in the comparator group was capped at 60 U. The effect was consistent across studies and across investigated subgroups.

In the studies, the FRC was always to be taken before breakfast, whereas the proposed SmPC states that Suliqua can be taken prior to any meal. It is acknowledged that both insulin glargine and lixisenatide may be taken at any time of the day when used in mono-therapy. The recommendation has been further supported by data from the lixisenatide file, showing that no statistically significant differences are observed between pre-breakfast or pre-dinner dosing of lixisenatide.

There is a lack of long-term data beyond 30 weeks with the FRC. However, further analyses have shown that only a small proportion of patients (7% and 15%, study EFC12404 and EFC12405 respectively) had both reached the maximum dose and were in need of intensified treatment at week 30. In addition, data from the lixisenatide file has been presented which shows maintenance of efficacy up to 76 weeks in combination with basal insulin. Thus it appears plausible that the effect can be maintained for a majority of patients at the doses

available.

2.5. Clinical safety

Patient exposure

The safety of FRC compared with insulin glargine alone and lixisenatide alone in T2DM was mainly studied in one active-controlled, open-label, 24 weeks, Phase 2 study (ACT12374) and two active-controlled, open-label, 30 weeks Phase 3 studies (EFC12404 and EFC12405).

Safety data was pooled in the following two datasets:

- *Phase 3 controlled study pool* (including study EFC12404 and EFC12405)
- *Phase 2/3 controlled study pool* (including study ACT12374, EFC12404 and EFC12405).

Safety analyses of the FRC compared with lixisenatide alone were based on the results of Study EFC12404.

Cumulative exposure of study treatment in the Phase 2/3 controlled study pool was 534 patients-years (N=995) for FRC and 542 patients-years (N=994) for insulin glargine, respectively. Total exposure to study medication by final lixisenatide dose at the end of the open-label treatment period in study EFC12404 was 124.6 patient-years (N=233) (Table 17).

Table 17 Overall exposure to study medication in the Phase 2/3 studies – safety population

	Phase 2/3 controlled study pool[1]		Phase 3 controlled study pool[2]		EFC12404	
	Fixed Ratio Combination (N=995)	Insulin Glargine (N=994)	Fixed Ratio Combination (N=834)	Insulin Glargine (N=832)	Fixed Ratio Combination (N=469)	Lixisenatide (N=233)
Cumulative exposure (patient-years)	533.6	542.5	461.8	468.2	261.5	124.6
Duration of study treatment (days)						
Number	992	992	831	830	468	232
Mean (SD)	196.5 (37.6)	199.8 (29.7)	203.0 (35.7)	206.1 (27.3)	204.1 (33.9)	196.1 (48.2)
Median	211.0	210.0	211.0	210.0	211.0	211.0
Min : Max	1 : 252	1 : 249	1 : 252	1 : 249	2 : 252	6 : 224
Cumulative duration of study treatment by category [n (%)]						
Missing duration	3 (0.3%)	2 (0.2%)	3 (0.4%)	2 (0.2%)	1 (0.2%)	1 (0.4%)
≥ 1 day	992 (99.7%)	992 (99.8%)	831 (99.6%)	830 (99.8%)	468 (99.8%)	232 (99.6%)
≥ 15 days	982 (98.7%)	986 (99.2%)	823 (98.7%)	825 (99.2%)	465 (99.1%)	228 (97.9%)
≥ 29 days	977 (98.2%)	979 (98.5%)	818 (98.1%)	819 (98.4%)	462 (98.5%)	225 (96.6%)
≥ 57 days	968 (97.3%)	977 (98.3%)	810 (97.1%)	817 (98.2%)	456 (97.2%)	218 (93.6%)
≥ 85 days	956 (96.1%)	975 (98.1%)	801 (96.0%)	815 (98.0%)	453 (96.6%)	215 (92.3%)
≥ 127 days	938 (94.3%)	967 (97.3%)	787 (94.4%)	807 (97.0%)	447 (95.3%)	211 (90.6%)
≥ 169 days	905 (91.0%)	920 (92.6%)	781 (93.6%)	802 (96.4%)	441 (94.0%)	209 (89.7%)
≥ 211 days	515 (51.8%)	401 (40.3%)	515 (61.8%)	400 (48.1%)	328 (69.9%)	143 (61.4%)

[1] Studies included: ACT12374, EFC12404 and EFC12405.
[2] Studies included: EFC12404 and EFC12405.

The majority of patients exposed to FRC were in the age of <50-<65 years (72%) in the Phase2/3 study pool. A substantial amount of patients in the age above 65 years was exposed to the FRC (28%). However, the total exposure to FRC in very elderly (>75 years) was low (n=34). This is reflected in the SmPC.

Patients below 18 years of age and patients with severe renal impairment were not included in the studies. This is reflected in the SmPC and uses in these populations are defined as “Missing information” in the RMP.

Adverse events

Common adverse event

In the Phase 3 Study pool, the percentage of patients experience at least one treatment emergent adverse event (TEAE) was comparable in the FRC and insulin glargine group (55% vs 50%) but slightly lower in subjects on FRC compared to subjects on lixisenatide (57% vs 67%; study EFC12404). Percentages and rates of TEAEs are presented in Table 18.

There were no new or unexpected adverse events in any of the treatment groups. The main difference in TEAE pattern between the treatment groups was that subjects in the FRC group compared to subjects on insulin glargine more often experienced GI symptoms (*nausea* [10.0% versus 2.3%], *diarrhoea* [7.0% vs 3.6%], *vomiting* [3.4% versus 1.1%]).

On the other hand, GI symptoms were less frequently reported among subjects on FRC compared to lixisenatide. *Nausea* was reported in 9.6% in patients on FRC vs 24.0% in patients on lixisenatide and *vomiting* was reported 3.2% vs 6.4% in these treatment groups, respectively.

The overall most common (≥5%) TEAE in subjects on FRC were *nausea* (10.0%), *diarrhea* (7.0%), *nasopharyngitis* (7.0%), *upper respiratory tract infection* (5.5%) and *headache* (5.4%). All these are, by the Applicant, proposed to be labelled in the SmPC section 4.8.

Table 18 Overall summary of TEAEs in the phase 3 controlled studies safety population

	Phase 3 controlled study pool[1]				EFC12404			
	Fixed Ratio Combination (N=834)		Insulin Glargine (N=832)		Fixed Ratio Combination (N=469)		Lixisenatide (N=233)	
	n (%)	Events (Rate per 100 PY[2])	n (%)	Events (Rate per 100 PY[2])	n (%)	Events (Rate per 100 PY[2])	n (%)	Events (Rate per 100 PY[2])
Patients with any TEAE	462 (55.4%)	1248 (265.81)	418 (50.2%)	1044 (219.48)	267 (56.9%)	738 (277.81)	157 (67.4%)	453 (358.10)
Patients with any serious TEAE	38 (4.6%)	44 (9.37)	37 (4.4%)	48 (10.09)	18 (3.8%)	21 (7.91)	9 (3.9%)	14 (11.07)
Patients with any TEAE leading to death	3 (0.4%)	3 (0.64)	5 (0.6%)	6 (1.26)	2 (0.4%)	2 (0.75)	1 (0.4%)	1 (0.79)
Patients with any TEAE leading to permanent treatment discontinuation	22 (2.6%)	24 (5.11)	12 (1.4%)	19 (3.99)	12 (2.6%)	14 (5.27)	21 (9.0%)	30 (23.71)

[1] Studies included: EFC12404 and EFC12405.
[2] Rate per 100 PY (patient years): calculated as 100*(number of events/total patient years of exposure). Each patient year's of exposure was calculated as time from the first to the last injection of IMP plus 3 days. Total patient years of exposure is 469.51 years for fixed ratio combination and 475.66 years for insulin glargine for Phase 3 controlled study pool, 265.65 years for fixed ratio combination and 126.5 years for lixisenatide for EFC12404 study.

Gastrointestinal events

The first event of *nausea* and *vomiting* was reported within approximately the first 9 weeks after the start of FRC. The majority of the patients that experienced *nausea* and *vomiting* had only 1 or 2 episodes of these events. Most (99%) of the events were of mild or moderate severity.

Hypoglycaemia

Due to the different populations, symptomatic hypoglycaemia was analysed separately for each Phase 3 study.

Overall, there was no sign of increased risk in frequency of patients who experienced at least one event of documented symptomatic hypoglycaemia (defined as an event with typical symptoms of hypoglycaemia accompanied by a measured plasma glucose concentration of ≤ 3.9 mmol/L [70 mg/dL]) in the FRC groups compared to patients on insulin glargine. Among insulin naïve patients (study EFC12404) 25.6% on FRC and 23.6% on insulin glargine respectively, experienced at least one event of documented symptomatic hypoglycaemia. The corresponding frequencies for patients insufficiently controlled on basal insulin with or without OAD were higher, 40.0% for patients on FRC and 42.5% for patients on insulin glargine.

The rate of documented symptomatic hypoglycaemic event per patient-year was 1.44 in the FRC group compared to 1.22 in the insulin glargine group in study EFC12404 and 3.03 in the FRC group compared to 4.22 in the insulin glargine group in study EFC12405.

As expected the risk for symptomatic hypoglycaemia was significantly increased for subjects on FRC compared to subjects in the lixisenatide group (6.4%).

No cases of severe hypoglycaemia were noted in the FRC subjects during the 30 week trial period in study EFC12404. In study EFC12405, severe hypoglycaemia was reported in low frequency in both patients on FRC (1.1%) and on insulin glargine (0.3%)..

Cardiovascular Events

There was no increased rate of CV events in subjects on FRC compared to subjects on the mono-components (insulin glargine and lixisenatide, respectively). The majority of CV events, both in the FRC and insulin glargine group, were events related to "*coronary revascularization procedures"*.

Pancreatitis

There were no events judged by the PSAC to be pancreatitis in any of the treatment groups. In accordance with the Article 5(3) of Regulation (EC) No. 726/2004 from CHMP in October 2013, of GLP-1 based therapies and pancreatic safety the RMP includes pancreatitis as an important identified risk and the SmPC section 4.4 includes a warning regarding acute pancreatitis.

Malignant or unspecified tumours

Malignant or unspecified tumors were presented in 7 (0.7%) patients in the FRC group, 5 (0.5%) patients in the insulin glargine group, and 1 (0.4%) patient in the lixisenatide group. There were no clinically relevant differences across treatment groups in malignant or unspecified tumours.

Medication errors

The number of pen-related events (PRE) per 100 PYE was in general slightly higher for subjects on FRC compared to both subjects on insulin glargine and lixisenatide, respectively. A further and deeper analyse of PRE is presented in the document "Pen-related events and initiation dose deviations observed in clinical trials" attached in Annex 12.2 in the RMP. According to this document the major reason for the PREs was events of category 1 ("Use of pen outside its intended dose range or outside the dose range defined by the study protocol"). None of the PREs in any of the treatment groups were associated with a clinical event.

"Medication errors including mix-ups between the different strength of the product" have been suggested as an important potential risk in the RMP. The risk includes *"Mix-up with different product strengths including by visually impaired or colour blind patient mix-ups".* A warning regarding mix-ups between the 2 strength of Suliqua and other injectable diabetes medicinal product is reflected in the PIL and SmPC (see also section 3.5 Risk management plan).

Treatment-emergent adverse events by investigator causality

In the Phase 3 study pool, the percentage of patients with at least 1 TEAE, judged by the Investigator to be related to IMP, was higher in the FRC compared with the insulin glargine group (14.6% versus 1.9%). In Study EFC12404, the percentage was lower in the FRC group compared with the lixisenatide group (14.9% versus 32.2%).

The most frequently reported drug-related TEAEs with an incidence ≥3% in any treatment group (ie, FRC, insulin glargine and/or lixisenatide groups) were *nausea* (8.4%, 0.1%, and 22.3%, respectively), *headache* (0.6%, 0.4%, and 4.3%, respectively), *diarrhea* (2.2%, 0.1%, and 3.0%, respectively), and *vomiting* (2.2%, 0%, and 3.9%, respectively). All these adverse reactions have been listed in the SmPC section 4.8 of the FRC with a frequency based on reactions judged as related by the investigator which is accepted.

Serious adverse events and deaths

Serious adverse events occurred in 4.6% of subjects on FRC and with similar frequencies as the monotherapies (FRC vs insulin glargine: 4.6% vs 4.4% [Phase 3 study pool] and FRC vs lixisenatide [study EFC12404]: 3.8% vs 3.9%). Thus, there seemed not to be an increased risk of SAEs in subject on FRC compared to subjects on the respective monotherapies. No apparent PT clustering of serious events was noted. Most PTs were reported with low frequencies. In the FRC group, no PT were reported in more than 2 cases. The most common SOC for SAEs was *Cardiac disorders* with 9 events (1.1%) in the FRC group and 8 events (1.0%) in the insulin glargine group.

In total, 10 fatal events were reported in the Phase 3 studies and none in the Phase 2 study or in the 6 Phase 1 studies. Three of the fatal events occurred in subjects on FRC, 6 in subjects on insulin glargine and one in a subject on lixisenatide. The fatal events were distributed without any apparent clustering of PTs or difference in frequency between the treatment groups.

Laboratory findings

Serum Calcitonin, haematology parameters (haemoglobin, haematocrit, erythrocytes, platelets, white blood cells), lipid parameters (total cholesterol, triglycerides, HDL-C, and LDL-C), electrolytes, renal function tests (creatinine clearance, creatinine, uric acid and albumin) and liver function tests (ALT, AST, ALP, GGT, and total bilirubin) were tested at baseline and through the on-treatment period without any relevant change from or difference between treatment groups.

Pancreatic enzymes (Lipase and amylase)

Overall, concentrations of both lipase and amylase slightly increase with FRC over 30 weeks of treatment.

Lipase levels increased more with FRC compared to use with insulin glargine but less compared to use with lixisenatide.

Amylase increased similar between the three treatment groups.

The percentage of patients in the FRC group with elevations in lipase or amylase considered as Potential Clinically Significant Abnormal (≥3 x ULN regardless of baseline status) were low, 7/828 (0.8%) for lipase and 4/468 (0.9%) for amylase. Almost equally low percentages of elevations considered as PCSA were seen for insulin glargine and lixisenatide.

Vital signs

Overall, there was no change of in SBP or DBP from baseline and through the on treatment period in any of the studied treatment groups.

Heart rate

Overall, heart rate increased slightly in all groups, most in the subjects on lixisenatide. The change from baseline after 30 weeks on treatment was 0.9±8.9 bpm in the FRC group, 0.7±8.6 bpm in the insulin glargine group and

1.8±8.9 bpm in the lixisenatide group. The number of PCSA heart rate cases was equally low in all treatment groups (one in each).

Previous studies have indicated that liraglutide (and other GLP 1RA) increases the heart rate and this is reflected in the SmPC section 4.8 for lixisenatide as monotherapy. Even if the present studies did not show any increased *heart rate* with the FRC, the known phenomenon with increased heart rate for lixisenatide (and other GLP 1RA) as monotherapy, is reflected in the SmPC even for the FRC.

Safety in special populations

No difference of clinical importance regarding incidence of TEAEs was noted between the subgroups of gender, BMI and race.

Age

Overall, the total percentages of TEAEs did not differ between the different age-groups (<65 versus ≥65 years and <75 versus ≥75 years, respectively). However, in the small group of very elderly (≥75 years; n=34) the risk of *nausea* and *diarrhoea* were increased compared to the subjects below 75 years (*nausea*: 9.4% vs 24.2% and *diarrhoea* 6.7% vs 12.1% respectively among patients <75 versus ≥75 years). Serious TEAEs were also more frequent in the age-group ≥75 years (27%) compared to the younger age groups < 50 years (3%), ≥ 50 to < 65 years (3%) and ≥ 65 to <75 (6%). However, the events in the very elderly populations were not considered as related to IMP and no fatal events occurred in this age group.

Use of lixisenatide as monotherapy has been studied in a larger population of the very elderly in study EFC12703 (GetGoal-O; EMEA/H/C/002445/II/0014) and in the ELIXA study (EMEA/H/C/002445/II/0013). Results from these studies indicated that the risks associated with lixisenatide treatment in the geriatric population (including patients >75 years) were not considerably increased compared with the risk associated with this treatment in the overall diabetic population. The benefit risk was thus considered to be positive also in this population.

Renal function

TEAE incidence in the FRC treatment group were similar in patients with normal renal function (53.8%) compared to mild renal function (56.5%). Patients on FRC with moderate decrease in GFR had higher percentage of TEAEs (76.5%) compared to those with normal GFR and mild decreased GFR. However, this patient group was small (n=37/995 on FRC in the Phase 2/3 controlled study pool) which makes a meaningful conclusion on clinical relevance difficult.

Use of lixisenatide as monotherapy in the population with moderately increased renal function was also, as age, studied in study EFC12703 (GetGoal-O; EMEA/H/C/002445/II/0014) and in the ELIXA study (EMEA/H/C/002445/II/0013). Data from these studies indicated that the risks associated with lixisenatide treatment in the population with moderately increased renal function were not considerably increased compared with the risk associated with this treatment in the overall diabetic population. The benefit risk was thus considered to be positive also in this population.

No patients with severe renal impairment were included in the studies. This is reflected in the SmPC section 4.2 and 4.4 and “Use in patients with severe renal function” are included in the RMP as “Missing information”.

Immunological events

Allergic reactions: Events adjudicated by ARAC as allergic reactions were reported in similar low frequencies between subjects on FRC (0.7%) compared to subjects in the insulin glargine (0.5%) and lixisenatide group

(0.9%). Three events in patients on FRC were judged as allergic reactions possible related to the treatment. All these events were events of *urticaria.* The Applicant has proposed urticaria to be included in the SmPC section 4.8 (uncommon) (Table 19).

Table 19 Number (%) of patients with TEAEs adjudicated as allergic reaction by ARAC in the Phase 2/3 controlled studies – safety population.

			Phase 2/3 controlled study pool[1]		EFC12404	
Relationship to Study Treatment (by ARAC)	ARAC Diagnosis Categories	MedDRA Coded Term (PT) for ARAC Diagnosis	Fixed Ratio Combination (N=995)	Insulin Glargine (N=994)	Fixed Ratio Combination (N=469)	Lixisenatide (N=233)
Total patient years of exposure			542.64	551.29	265.65	126.50
All	Any category	Any event	7 (0.7%)	5 (0.5%)	6 (1.3%)	2 (0.9%)
	Urticaria (hives)	Urticaria	3 (0.3%)	1 (0.1%)	3 (0.6%)	1 (0.4%)
	Angioedema	Angioedema	3 (0.3%)	0	3 (0.6%)	0
	Anaphylactic reaction	Anaphylactic reaction	0	0	0	1 (0.4%)
	Other	Any event	1 (0.1%)	4 (0.4%)	0	0
		Rhinitis allergic	1 (0.1%)	4 (0.4%)	0	0
		Conjunctivitis allergic	0	1 (0.1%)	0	0
Possibly related to IMP	Any category	Any event	3 (0.3%)	0	3 (0.6%)	2 (0.9%)
	Urticaria (hives)	Urticaria	3 (0.3%)	0	3 (0.6%)	1 (0.4%)
	Anaphylactic reaction	Anaphylactic reaction	0	0	0	1 (0.4%)

Injection site reactions: The frequency of subjects reporting injection site reactions were similar with the FRC compared to formulations with insulin glargine (1.7% [17/995] vs 1.1% [11/994]) and FRC compared to lixisenatide, respectively (2.6% [127469] vs 3.0% [7/233]). The events were mild in all treatment groups, except for one event in the FRC and one in the insulin glargine group with moderate severity (Table 20).

Mostly single episodes of injection site reactions were reported (15/17 in the FRC group).

Table 20 Number (%) of patients with TEAEs related to injection site reactions in the Phase 2/3 controlled studies – safety population.

	Phase 2/3 controlled study pool[1]		EFC12404	
	Fixed Ratio Combination (N=995)	Insulin Glargine (N=994)	Fixed Ratio Combination (N=469)	Lixisenatide (N=233)
Number (%) of patients with events	17 (1.7%)	11 (1.1%)	12 (2.6%)	7 (3.0%)
Total patient years at risk	536.10	547.14	260.70	123.67
EAIR per 100 patient years	3.17	2.01	4.60	5.66
Exposure adjusted Relative Risk (95% CI vs comparators)	1.57 (0.73, 3.46)		0.81 (0.32, 2.20)	

Antibody status and concentration over time

Anti-lixisenatide antibodies (ADA) status and concentrations were studied in study EFC12404 and study EFC12405. Development of ADA (e.g. conversion from ADA negative to ADA positive) occurred in 36% of the subjects on FRC over 30 weeks of treatment. A higher converting rate, 48%, was noted for the subjects using lixisenatide.

In study EFC11321 a placebo-controlled, study to compare lixisenatide treatment (as mono-component) with placebo in T2DM patients not adequately controlled by a stable dose of metformin with or without sulfonylurea (EMEA/H/C/2445/MEA/002), the mean reduction in HbA1c was smaller in the group with the highest antibody concentrations. In the present Phase 3 program most of the subjects, 79%, both on FRC and lixisenatide respectively, had after 30 weeks treatment, ADA concentrations below the lower limit of quantification (LLOQ<3.21nmol/L). The remaining 21%, had concentrations of ADA above LLOQ.

Anti-insulin antibodies (AIA): In the population without prior treatment to insulin (study 12404), the rate of conversion from AIA negative status at baseline to positive status at Week 30, was higher in the FRC group compared with the insulin glargine group: 18.9% versus 8.9%. In patient earlier treated with basal insulin (study 12405) the increase was lower and more similar between the treatment groups (15% in the FRC group vs 12% in the insulin glargine group) (Table 21).

In accordance in patients without prior insulin treatment (study 12404) the AIA titers were higher among patient on FRC compared to these on only insulin glargine (Table 22).

The Applicant has in addition to AIA data or study 12404 presented and discussed comparable side-by side data between treatment with insulin glargine (Lantus) respectively FRC from the FRC Phase 2 study (ACT12374), in insulin naïve patients. Also data from the Phase 3 studies of lixisenatide (study EFC10781) with lixisenatide+insulin glargine *vs* insulin glargine (Lantus) has been submitted. These data shows a slight higher incidence of AIA positive subjects in the FRC (43%) or insulin glargine + lixisenatide patients (17%) compared to patients only treated with insulin glargine (33% and 12% respectively) after 24 weeks treatment. The median AIA titres were in general low (varying from 2-8 in both studies). No clinically relevance regarding safety of subjects with AIA positivity in general has been identified.

Immunogenicity/neutralisation is defined as an important potential risk in the RMP for SULIQUA and general warning regarding antibody formation against insulin glargine and/or lixisenatide is proposed in SmPC section 4.4 of SULIQUA.

Table 21 Number (%) with AIA status by visit during the on-treatment period in the Phase 3 controlled studies EFC12404 and EFC12405 – Safety population

		EFC12404		EFC12405	
Visit	Anti-insulin Glargine Antibody Status, n/N1(%)	Fixed Ratio Combination (N=469)	Insulin Glargine (N=467)	Fixed Ratio Combination (N=365)	Insulin Glargine (N=365)
Baseline	Positive	2/436 (0.5%)	1/451 (0.2%)	42/339 (12.4%)	51/339 (15.0%)
	Negative	434/436 (99.5%)	450/451 (99.8%)	297/339 (87.6%)	288/339 (85.0%)
Week 30	Positive	90/428 (21.0%)	38/426 (8.9%)	86/328 (26.2%)	87/351 (24.8%)
	Negative	338/428 (79.0%)	388/426 (91.1%)	242/328 (73.8%)	264/351 (75.2%)
	Conversion from negative at baseline to positive	81/428 (18.9%)	38/426 (8.9%)	50/328 (15.2%)	40/351 (11.4%)
Last on-treatment value	Positive	90/447 (20.1%)	39/440 (8.9%)	88/347 (25.4%)	88/355 (24.8%)
	Negative	357/447 (79.9%)	401/440 (91.1%)	259/347 (74.6%)	267/355 (75.2%)
	Conversion from negative at baseline to positive	81/447 (18.1%)	39/440 (8.9%)	51/347 (14.7%)	41/355 (11.5%)

N = the number of patients in the Safety population.
N1 = the number of patients with available anti-lixisenatide antibody status in the Safety population at the respective visit.
On-treatment period for anti- insulin glargine anti-body is defined as the time from the first dose of open-label investigational medicinal product (IMP) up to 28 days after the last dose administration.
PGM=PRODOPS/AVE0010/OVERALL_LIXILAN/CTD_2015/REPORT/PGM/ab_byvisit_status_t.sas OUT=REPORT/OUTPUT/ab_byvisit_status_t_insulin_p3_i.rtf (12NOV2015 - 5:23)

Table 22 AIA titres (1/x) during the on treatment period in Phase 3 studies – safety population

Visit	EFC12404		EFC12405	
	Fixed Ratio Combination (N=469)	Insulin Glargine (N=467)	Fixed Ratio Combination (N=365)	Insulin Glargine (N=365)
Baseline				
Number	2	1	42	51
Geometric mean	45.255	8.000	14.254	13.967
CV%	140.8700	NC	107.8018	296.8005
Median	513.000	8.000	16.000	16.000
Q1 : Q3	2.000 : 1024.000	8.000 : 8.000	8.000 : 32.000	4.000 : 32.000
Min : Max	2.00 : 1024.00	8.00 : 8.00	2.00 : 128.00	2.00 : 1024.00
Week 30				
Number	90	38	86	87
Geometric mean	11.668	8.450	8.130	9.841
CV%	305.7801	201.9557	277.1301	234.5548
Median	8.000	8.000	8.000	8.000
Q1 : Q3	4.000 : 32.000	2.000 : 16.000	4.000 : 16.000	4.000 : 16.000
Min : Max	2.00 : 1024.00	2.00 : 256.00	2.00 : 512.00	2.00 : 512.00

Safety related to drug-drug interactions and other interactions

No additional or special studies have been conducted with the insulin glargine/lixisenatide combination to evaluate the effects on other drugs. Data relays on the lixisenatide monotherapy program.

In the insulin glargine/lixisenatide FRC phase 3 studies, no patients were allowed to use SU, thus there is no experience of concomitant use with the FRC with SU. In general, concomitant use of SU with antidiabetic products, including GLP-1 RA and insulin, is associated with an increased risk for hypoglycaemia and the SmPC for lixisenatide already recommends against the use of the triple combination of SU, lixisenatide and insulin.

Discontinuation due to adverse events

The frequency of patients with permanent discontinuation of study treatment due to TEAEs was higher in the FRC group (2.6%; both in the Phase 3 study pool and in study 12404) compared to monotherapy with insulin glargine (1.4%) but lower compared to monotherapy with the lixisenatide (9.0%). The difference between treatment groups was largely due to different frequencies of AEs in the SOC *gastrointestinal disorders* (nausea 0.7%, vomiting 0.2%, diarrhoea 0.1% for the FRC vs none for insulin glargine) but included also events of *urticarial* (0.4% vs 0, for the FRC and insulin glargine respectively).

2.5.1. Discussion on clinical safety

The percentage of patients experience at least one TEAE was comparable in the FRC and insulin glargine group (55% vs 50% in the Phase 3 Study pool) but slightly lower in subjects on FRC compared to subjects on lixisenatide (57% vs 67% in study EFC12404).

Overall, there were no unexpected adverse events in any of the treatment groups detected compared to the known adverse reactions with the mono-components.

The overall most common adverse reactions with FRC, with a frequency above 5 % and irrespective of investigator causality assessment were, apart from *hypoglycaemia* (see further below), *nausea* (10.0%), *diarrhoea* (7.0%), *nasopharyngitis* (7.0%), *upper respiratory tract infection* (5.5%) and *headache* (5.4%).

The most common treatment emergent adverse reactions reported as related to study drug (FRC) by the investigator were *nausea* (8.4%), *diarrhoea* (2.2%), *vomiting* (2.2%) and *dizziness* (1.4%). These four reactions are all labelled in the SmPC section 4.8 as "common" based on these frequencies.

The main difference in TEAE pattern between the treatment groups was that subjects in the FRC group compared to subjects on insulin glargine more often experienced GI symptoms (incidence of *nausea* [10.0% versus 2.3%], *diarrhoea* [7.0% vs 3.6%]*, vomiting* [3.4% versus 1.1%]) but patients on FRC less often experienced these reactions compared to subjects on lixisenatide (*nausea*:9.6% vs 24.0%; *vomiting*: 3.2% vs 6.4% and *headache:* 5.1% vs 7.7%, respectively).

Serious adverse events occurred in 4.6% of subjects on FRC and with similar frequencies as the monotherapies (FRC vs insulin glargine, 4.6% vs 4.4% and FRC vs lixisenatide, 3.8% vs 3.9%). Most of the PTs of the SAEs were reported with low frequencies without any clustering.

Hypoglycaemia

There were similar percentages of patients experience at least one documented hypoglycaemic episode among insulin naïve patients (study EFC12404) in the FRC and insulin glargine group (25.6% and 23.6%, respectively). The corresponding percentage compared to subjects on lixisenatide was lower (6.4%). Most of the subjects, both on FRC and insulin glargine, experienced 1-3 episodes documented hypoglycaemic per patient.

For patients earlier treated with basal-insulin (study EFC124045) the percentages of at least one documented hypoglycaemic episode were higher in both treatment groups (40.0% [FRC] and 42.5% [insulin glargine]). Most probably this reflects that patients within study EF 12405 were more advanced in the diseases compared to the population in study EFC 12404.

Severe hypoglycaemia was reported in low frequency in both patients on FRC (1.1% [study 12405]) and in the insulin glargine group (0.3%).

It is known that concomitant use of SU with antidiabetic products, including insulin and GLP-1 RA, is associated with an increased risk for hypoglycaemia. However, in the present studies concomitant use with SU was not allowed. The SmPC for lixisenatide includes warnings against the use of the triple combination of SU, lixisenatide and insulin.

Medication errors

The FRC is provided in two different pens with two different ratios between insulin glargine and lixisenatide which may increase the risk for medication errors.

"Medication errors including mix-ups between the different strength of the product" have been suggested as an important potential risk in the RMP. The risk includes *"Mix-up with different product strengths including by visually impaired or colour blind patients mix-ups".* A warning regarding mix-ups between the 2 strength of Suliqua and other injectable diabetes medicinal product is reflected in the PIL and SmPC (see also section 5.1 Risk management plan – safety specification).

In order to high-light that Suliqua consists of two active substances and to avoid confusion, the term "dose steps" is used instead of "units". This is in line with the terminology used for the already approved product Xultophy.

Heart rate

A minor increase in heart rate was noted in all treatment groups (changes from baseline after 30 weeks were 0.9±8.9 bpm in the FRC group, 0.7±8.6 bpm in the insulin glargine group and 1.8±8.9 bpm in the lixisenatide group). The number of PCSA heart rate cases was equally low in all treatment groups (one in each).

Even if the present studies did not show any increased *heart rate* with the FRC, the known phenomenon with increased heart rate for lixisenatide (and other GLP 1RA) as monotherapy, is reflected in the SmPC section 4.8 of FRC.

Allergic reactions

Adjudicated allergic reactions by ARAC were reported in similar low frequencies between subjects on FRC compared to subjects in the insulin glargine (0.7% vs 0.5%) and lixisenatide (1.3% vs 0.9%). The PT:s of event judged as related to IMP (FRC) were all *urticaria. Urticaria* is labelled in the SmPC section 4.8. *Hypersensitivity* is defined as an important identified risk in the RMP based on information of insulin glargine and lixisenatide as mono-components.

Injection site reactions

The frequency of subjects reporting *injection site reactions* were similar with FRC compared to formulations with insulin glargine (1.7% vs 1.1%) and lixisenatide (2.6% vs 3.0%) as mono-components. Most of the events were mild in all treatment groups and mostly 1 episode was reported per subjects.

Anti-lixisenatide antibodies (ADA) and anti-insulin antibodies (AIA)

Development of ADA occurred in 36% of the subjects on FRC over 30 weeks of treatment compared to 48% in subjects on lixisenatide (EFC12404). However, most of the ADA positive subjects (79%) had low titres, below the lower limit of quantification.

After 30 weeks treatment, the insulin naïve population on FRC (study EFC12404) more often developed AIA (19%) compared to subjects on only insulin glargine (9%). In the non-insulin naïve patients (study EFC12405) the increase was lower and more similar between the treatment groups (15% in the FRC group vs 12% in the insulin glargine group).

It was also noted a slight increase in frequency of AIA in insulin naïve patients treated with FRC (43%) in the Phase 2 study (ACT12374) and with glargine + lixisenatide (17%) in the lixisenatide phase 3 study (EFC10781), compared to 33% (study ACT12374) and 12% (study EFC10781) in patients only treated with insulin glargine after 24 weeks of treatment.

The median AIA titres were, in generally comparable low in all studies with FRC, insulin glargine + lixisenatide and insulin glargine alone. No clinically relevance regarding safety of subjects with AIA positivity has in general been identified.

A general warning regarding antibody formation against insulin glargine and/or lixisenatide is also proposed, by the Applicant, in SmPC section 4.4. *Immunogenicity/neutralization* is, by the Applicant, suggested as an important potential risk in the RMP.

Use in special populations

Age: Overall, the total percentages of TEAEs did not differ between the different age-groups. However, in the small group of very elderly (≥*75* years; n=34) the risk of *nausea* and *diarrhoea* were increased compared to the subjects below 75 years (*nausea*: 9.4% vs 24.2% in patients <75years vs ≥75 years respectively and *diarrhoea*

6.7% vs 12.1% in these age groups). The incidence of serious TEAEs in the age ≥75 years were higher (27%) compared younger age groups (3-6%). Most of the serious TEAEs in the elderly population were judged as not related to the studied drug and no fatal events were presented in this age group.

Use of lixisenatide as monotherapy has earlier been studied in a larger population of the very elderly (in study EFC12703 and in the ELIXA study (EMEA/H/C/002445/II/0013). Results from these studies indicated that the risks associated with lixisenatide treatment in the geriatric population (including patients >75 years) were not considerably increased compared with the risk associated with this treatment in the overall diabetic population. The benefit risk was thus considered to be positive also in this population.

A limited use of the insulin glargine/lixisenatide FRC in patients above 75 years is reflected in the SmPC.

Renal impairment: Patients on FRC with moderate decrease in GFR had higher percentage of TEAEs (76.5%) compared to those with normal GFR (53.8%) and mild decreased GFR (56.5%). However, the population of patients with moderate renal impairment was small (n=37) in the present studies.

Use of lixisenatide as monotherapy in the population with moderately increased renal function was also studied in study EFC12703 and in the ELIXA study. Data from these studies indicated that the risks associated with lixisenatide treatment in the population with moderately increased renal function were not considerably increased compared with the risk associated with this treatment in the overall diabetic population. The benefit risk was thus considered to be positive also in this population.

No patients with severe renal impairment were included in the studies. This is reflected in the SmPC section 4.2 and 4.4 and "Use in patients with severe renal function" are included in the RMP as "Missing information".

2.5.2. Conclusions on clinical safety

No new or unexpected adverse reactions were noted with the fixed combination of lixisenatide/insulin glargine (FRC) compared to the mono-components. The adverse reaction patterns differed however in the aspect that the FRC group had a lower frequency of subjects with gastrointestinal adverse reactions compared to the lixisenatide group but a higher frequency of subjects with these reactions compared to use with insulin glargine. The incidences of documented hypoglycaemic episode were comparable between the FRC and insulin glargine group. However, it should be noted that concomitant use of SU was not allowed in the present studies with FRC.

Immunological reactions such as *allergic reactions* and *injections site reactions* were few and equally distributed between the different treatment groups. A lower frequency of patients developed lixisenatide antibodies (ADA) in the FRC group (36%) compared to the lixisenatide group (48%). However, development of insulin antibodies (AIA) after 30 weeks of treatment in insulin naïve patients was higher in subjects on FRC (19%) compared to subjects using insulin glargine as monotherapy (9%) in study 12404. This difference was not seen in the population with earlier exposure to insulin (study 12505; 15% AIA positives in the FRC group *vs* 12%in the insulin glargine group after 30 weeks treatment). The titres of AIA were however in general low in all treatment groups and no safety issues have been noted among the AIA positive subjects.

Overall, the fixed combination of lixisenatide/insulin glargine demonstrates a comparable safety profile as the two mono-components.

The RMP adequately reflects the safety concerns listed for the two monocomponents. The only risk specifically related to the FRC is *"Medication errors including mix-ups between the different strength of the product"*, which is included in the RMP as an important potential risk.

2.6. Risk Management Plan

Safety concerns

Important identified risks	Gastrointestinal events ie, nausea and vomiting
	Hypersensitivity reactions
	Hypoglycemia
	Pancreatitis
Important potential risks	Malignant neoplasm
	Pancreatic cancer
	Medullary thyroid cancer
	Medication errors including mix-ups between the different strength of the product
	Immunogenicity/neutralization
	Dehydration/acute renal impairment
	Teratogenicity
Missing information	Use in pregnancy and lactation
	Use in children and adolescents <18 years
	Use in patients with severe renal impairment (with or without low body weight)

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
SULIQUA				
EFC13794: A 26-week open-label study assessing the efficacy and safety of the insulin glargine/lixisenatide combination in adults with type 2 diabetes inadequately controlled on GLP-1 receptor agonist and metformin ± pioglitazone	To demonstrate the superiority of the insulin glargine/lixisenatide combination versus GLP-1 receptor agonist in HbA1c change from baseline to week 26.	Additional safety information for all relevant important identified and potential risks	Ongoing	Final study report planned: Q3 2018
Knowledge and understanding survey regarding the educational materials provided to the HCP population prescribing and dispensing SULIQUA and to the patient population treated with SULIQUA (cross-sectional survey)	To assess descriptively the knowledge and understanding of HCPs who prescribe or dispense SULIQUA and of patients treated with SULIQUA about the key safety messages in the HCP and patient guide, respectively, To assess the trends in knowledge and	Medication errors including mix-ups between the different strength of the product	Planned	Protocol to be submitted for review 6 months post-approval. Date for final study report to be determined and will be provided when the study protocol is finalized and approved.

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
	understanding of the educational materials among HCP and patient population over time.			
Lixisenatide/ GLP-1 receptor agonists				
EFC11476: Safety and efficacy study of lixisenatide as monotherapy and add on treatment to metformin and/or basal insulin in pediatric patients with T2DM.	To assess the efficacy and safety of lixisenatide as monotherapy and add on treatment to metformin and/or basal insulin for the treatment of T2DM in pediatric patients aged between 10 and less than 18 years.	Use in children and adolescents <18 years	Planned (start in Q4 2018)	Final report in Q1 2024
Pharmacoepidemiology study: Database study of GLP-1 receptor agonists and risk of acute pancreatitis, pancreatic cancer and thyroid cancer, in particular medullary thyroid cancer	A retrospective database study will be conducted using the existing national databases and registers in Sweden, Denmark, and Norway. The incidence rates of acute pancreatitis, pancreatic cancer, and thyroid cancer will be estimated among adult T2DM patients treated with GLP-1 receptor agonists (ie, exenatide & liraglutide) versus the ones treated with other anti-diabetics.	Acute pancreatitis, pancreatic cancer, and thyroid cancer, in particular medullary thyroid cancer.	Ongoing	Final report in Q3 2016
Pharmacoepidemiology study: Patient registry of lixisenatide use in adult type 2 diabetes	A registry to monitor the occurrences of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult type 2 diabetes patients treated with lixisenatide using the data from national registers and databases in Denmark, Norway and Sweden.	Acute pancreatitis, pancreatic cancer, and thyroid cancer, in particular medullary thyroid cancer.	Ongoing	Annual interim reports Final report in 2018 for acute pancreatitis and 2019 for cancer events of interest
Insulin glargine				
None				

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports

GLP-1: Glucagon-Like Peptide-1; HCP: Healthcare Professional; T2DM: Type 2 Diabetes Mellitus.
All pharmacovigilance studies are category 3 studies.

Risk minimisation measures

Safety concern	Routine risk minimization activities	Additional risk minimization activities
Important identified risks		
Gastrointestinal events ie, nausea and vomiting	Prescription only medicine; Addressed in SmPC section 4.8 Undesirable effects; Addressed in PIL section 2. What you need to know before you use Suliqua and section 4. Possible side effects.	None
Hypersensitivity reactions	Prescription only medicine; Addressed in SmPC sections 4.3 Contraindications; 4.8 Undesirable effects; Addressed in PIL section 2. What you need to know before you use Suliqua and section 4. Possible side effects.	None
Hypoglycemia	Prescription only medicine; Addressed in SmPC sections 4.4 Special warnings and precautions for use; 4.5 Interaction with other medicinal products and other forms of interaction; 4.7 Effect on ability to drive and use of machines; 4.8 Undesirable effects. Addressed in PIL section 2. What you need to know before you use Suliqua and section 4. Possible side effects.	None
Pancreatitis	Prescription only medicine; Addressed in SmPC sections 4.4 Special warnings and precautions for use. Addressed in PIL section 2. What you need to know before you use Suliqua.	None
Important potential risks		
Malignant neoplasm	Prescription only medicine.	None
Pancreatic cancer	Prescription only medicine.	None
Medullary thyroid cancer	Prescription only medicine.	None
Immunogenicity/neutralization	Prescription only medicine; Addressed in SmPC section Section 4.4 of SmPC Special warning and precautions for use.	None
Dehydration/acute renal impairment	Prescription only medicine; Addressed in SmPC sections 4.2 Posology and method of administration; 4.4 Special warnings and precautions for use; 5.2 Pharmacokinetic properties. Addressed in PIL section 2 What you need to know before you use Suliqua.	None
Teratogenicity	Prescription only medicine; Addressed in SmPC sections 4.6 Fertility, pregnancy and lactation; 5.3 Preclinical safety.	None
Medication errors including mix ups between the different strength of the product	Prescription only medicine; Use of an adequate pen qualification to present the dose range after the trade name to identify the two different pens of Suliqua. The adequate pen qualification (10-40) or (30-60) is noted in the SmPC, the PIL and the IFU and presented as highlight on the outer packaging and the pen label; Addressed in SmPC sections 2 Qualitative and Quantitative Composition; 4.2 Posology and method of administration;	HCP guide and Patient guide

Safety concern	Routine risk minimization activities	Additional risk minimization activities
	4.4 Special warnings and precautions for use; 6.6 Special precautions for disposal and other handling. Addressed in PIL section 2. What you need to know before using Suliqua and section 3 How to use Suliqua and section 6 Contents of the pack and other information. Addressed in the IFU.	
Missing information		
Use in pregnancy and lactation	Prescription only medicine; Addressed in SmPC sections 4.6 Fertility, pregnancy and lactation; 5.3 Preclinical safety data. Addressed in PIL section 2. What you need to know before you use Suliqua.	None
Use in children and adolescents <18 years	Prescription only medicine; Addressed in SmPC sections 4.2 Posology and method of administration; 5.2 Pharmacokinetic properties. Addressed in PIL section 2. What you need to know before you use Suliqua.	None
Use in patients with severe renal impairment (with or without low body weight)	Prescription only medicine; Addressed in SmPC sections 4.2 Posology and method of administration; 4.4 Special warning and precautions for use; 5.2 Pharmacokinetic properties. Addressed in PIL section 2. What you need to know before you use Suliqua and section 3 How to use Suliqua.	None

SmPC: Summary of Product Characteristics; PIL: Patient Information Leaflet; IFU: Instructions for Use.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. 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.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Suliqua (insulin glargine / lixisenatide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this

medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The insulin glargine/lixisenatide combination Suliqua is a fixed ratio combination (FRC) product of a long-acting human insulin analogue (insulin glargine) together with a glucagon like peptide-1 (GLP-1) receptor agonist (lixisenatide). The Applicant has developed two pens in order to accommodate both the expected dose range for insulin glargine as well as the dose range for lixisenatide, thus to avoid exceeding the maximum dose of 20 µg lixisenatide. When a patient switches from Pen A to Pen B, without changing the insulin dose, this will lead to a decrease in the lixisenatide dose by a maximum of 7 µg (at an insulin dose of 40 U). The maximum dose is 60 U/20 µg and the dose is to be individually titrated based on the insulin need.

The efficacy of the fixed-ratio combination in patients with T2DM was assessed in two pivotal phase 3 active-controlled, 30-week, open-label studies in patients with type 2 diabetes mellitus (T2DM); study EFC12404 and study EFC12405. The studies included in total 1906 patients. Both studies were in general adequately designed and largely in line with the current EMA guideline on fixed combinations (CHMP/EWP/240/95 Rev. 1). There are no concerns with regards to the general conduct of the studies.

Study **EFC12404** was designed to evaluate the contribution of the respective components insulin glargine and lixisenatide to the effect of the FRC. This study only included patients who were insulin naïve. Study **EFC12405** evaluated the FRC in patients on previous basal insulin therapy, with insulin glargine as the active comparator. Thus this study was designed to support the use of the FRC in patients switching from a therapy which included basal insulin. In both studies, the only concomitant oral anti-diabetic treatment allowed was metformin.

Baseline data show that the subjects included can be considered representative for a T2DM population failing on OAD treatment and that would benefit from insulin initiation in study **EFC12404**. Baseline data from study **EFC12405** show that subjects that can be considered representative for a T2DM population on basal insulin treatment were included.

Both studies met their primary objective. In study **EFC12404,** superiority of the FRC over lixisenatide was shown as well as over insulin glargine. The change in HbA1c from baseline was -1.63 % in the FRC treated group. The treatment difference in change in HbA1c between FRC and insulin glargine was -0.29% (95% CI [-0.38% to -0.19%]; p< 0.0001), whereas the treatment difference between FRC and lixisenatide was -0.78% (95% CI [-0.90% to -0.67%]; p< 0.0001). The primary outcomes are considered statistically convincing. In study **EFC12405**, the change in HbA1c from baseline in the FRC group was -1.13% and -0.62% the insulin glargine group, with a treatment difference of -0.52% (95% CI [-0.63% to -0.40%]; p< 0.0001). It appears as if the maximal effect has been reached at six months for both treatments.

In both studies the insulin dose was capped at 60 U per day in the comparator arm. This is adequate in study **EFC12404**, where the main objective was to study the contribution of each component to the effect of the FRC. There were no difference in insulin doses between the FRC and insulin treated groups at week 30. The mean daily dose rose concordantly over the treatment period. The distribution of patients across different dose levels was comparable. A slightly higher proportion of patients in the insulin glargine group (20.1 %) used 60 U at week 30 compared to the FRC group (15.6 %).

However, in study **EFC12405**, the capping of the insulin glargine dose at 60 U per day is of some concern as the main objective was to compare the FRC with basal insulin treatment. Thus capping the insulin dose in the

comparator arm may not allow optimising the insulin treatment. However, at the end of the 30 week study period, the insulin dose did not differ between groups (mean dose about 47 U, 0.54 U/kg body weight, in both groups). A slightly higher proportion of patients in the insulin glargine treated group (31%) was using the maximum dose allowed (60 U) than in the FRC treated group (27%). Taking the low proportion of patients needing rescue in both study arms (2.7% [10/366] for FRC and 6.0% [22/365] for insulin glargine), the capping of the insulin glargine dose appears not to have affected the outcome to a greater extent in this short-term study and the lower need for rescue may be seen as additional support for FRC superiority in this setting. However, no conclusions can be drawn for the FRC in comparison to insulin glargine when insulin glargine is used without limitations.

In both studies, the majority of patients were using a lixisenatide dose of ≥15 µg to ≤20 µg, thus very close to the recommended maintenance dose of lixisenatide when used as monotherapy. In study **EFC12404**, the mean lixisenatide dose in the monotherapy group was not calculated, but 89 % of patients were receiving the recommended maintenance dose of 20 µg.

FPG was comparable across treatment groups at baseline in both studies. In study **EFC12404**, at week 30, the effect on FPG was comparable in the FRC and insulin glargine treated groups, and mean values were well within the target range (6.32 mmol/L and 6.53 mmol/L, respectively). For lixisenatide the FPG at week 30 was 8.27 mmol/L (estimated treatment difference vs FRC -1.96 mmol/L, 95%CI [-2.25 to -1.68]; p<0.0001). In study **EFC12405**, the decrease in FPG was less pronounced than in study EFC12404, probably due to the titration of insulin in the screening phase, with a mean FPG at week 30 within target for both groups (6.78 mmol/L and 6.69 mmol/L, respectively).

In both studies, the effect on PPG excursions was studied during a standardized meal test. In study **EFC12404**, a greater change in mean 2-hour PPG excursions from baseline was observed for the FRC treated group (-2.31 mmol/L) compared to the insulin glargine treated group (-0.2 mmol/L). The treatment difference was statistically significant (-2.1 mmol/L, 95%CI, -2.5 to -1.8; p<0.0001). The corresponding change in mean 2-hour PPG excursion for lixisenatide was -3.23 mmol/L. In line with the FPG data, the pre-meal PG was comparable and lower in the FRC and insulin glargine treated groups compared to the lixisenatide group. In study **EFC12405**, a decrease of -3.9 mmol/L in the mean 2-hour PPG excursions was observed for the FRC treated group compared to -0.5 mmol/L in the insulin glargine treated group. The treatment difference was statistically significant (-3.4 mmol/L, 95%CI [-3.92 to -2.94]; p<0.0001). In both studies, the highest PPG was observed 1 hour after the meal with FRC and lixisenatide, whereas PPG had not started to decline at 2 hours in the insulin glargine treated groups.

Across both studies, there was a notable reduction in SMPG profiles with all three treatments compared to baseline. The decrease in the average 7-point SMPG was larger in the FRC treated group compared to both the lixisenatide and insulin glargine treated groups and the treatment differences were statistically significant. Compared to insulin glargine, the FRC treated group showed lower pre- and post-prandial values at all time points except for the pre-breakfast (FPG) value. This appears to be mainly driven by a lower PPG excursion after breakfast with FRC. The PPG excursions after lunch and dinner appear comparable between treatments, but due to the lower pre-lunch values in the FRC, all PG values remained lower than those observed in the insulin glargine treated group.

Thus the data on 2-hour PPG excursions, FPG and SMPG profiles are consistent and indicate that the insulin component mainly affects the FPG levels and the lixisenatide exerts its main effect on PPG levels.

In both studies, body weight remained stable or decreased slightly in the FRC treated group (-0.3 kg (study **EFC12404**); -0.67 kg (study **EFC12405**)) whereas body weight increased in the insulin glargine group (1.1 kg

(study **EFC12404**); 0.70 kg (study **EFC12405**)) and decreased in the lixisenatide group (-2.3 kg (study **EFC12404**)). The treatment difference between FRC and insulin glargine was statistically significant in both studies.

In study **EFC12404**, which included insulin-naïve subjects, the proportion of patients reporting symptomatic hypoglycaemias was rather low and comparable in the FRC (25.6 %) and insulin glargine (23.6 %) treated groups. As expected, the rate of hypoglycaemias was lowest in the lixisenatide group (6.4 %). In study **EFC12405**, which included subjects already on basal insulin, the proportion of patients reporting symptomatic hypoglycaemias was higher than in study **EFC12404** but still comparable between the groups (40% with FRC and 43% with insulin glargine). Few episodes of severe symptomatic hypoglycaemia were reported (4 patients in the FRC group and 1 in the insulin glargine group).

The responder analyses support the findings. In study **EFC12404**, the proportion of patients achieving both the target of < 7% and ≤ 6.5% was higher in the FRC treated group (74 % and 56 %, respectively) compared to both insulin glargine (59 % and 40 %, respectively) and lixisenatide (33 % and 19 %, respectively). A statistically significantly higher proportion of patients reached the target "HbA1c < 7 % with no body weight gain" in the FRC group (43.2%) compared to the insulin glargine group (25.1%). The proportion was also higher in the FRC group compared to the lixisenatide group (27.9%). A higher proportion of patients in the FRC group (31.8%) reached the triple composite endpoint "HbA1c < 7%, no body weight gain and no documented symptomatic hypoglycaemias" compared to both the insulin glargine group (18.9%) and the lixisenatide group (26.2%). The treatment difference between FRC and insulin glargine was statistically significant. In study **EFC12405**, the proportion of patients with HbA1c value <7% or ≤ 6.5% at Week 30 respectively, were higher in the FRC treated group (55% and 34%, respectively) compared to the insulin glargine treated group (30% and 14%, respectively). A statistically significant higher proportion of patients treated with the FRC reached the composite endpoint of "HbA1c <7% with no body weight gain" (34.2%) compared to the insulin glargine treated group (13.4%). The proportion of patients who achieved the triple composite endpoint "HbA1c <7% without body weight gain and no documented symptomatic hypoglycaemia" was also higher in the FRC treated group (20%) than in the insulin glargine treated group (9%).

The efficacy data in the subgroup of patients switching from monotherapy with basal insulin to the FRC in study EFC12405 (41 patients in the FRC group), was consistent with the data obtained in the overall population. The mean change in HbA1c was -1.27% in the FRC-treated group And the responder rate (HbA1c <7%) was 56.1%.

Uncertainty in the knowledge about the beneficial effects

The FRC has only been studied in patients on a background metformin treatment as all other OADs were discontinued at screening. Further to this, the only external support for the triple combination with other OADs comes from the lixisenatide file where the triple combination SU/lixisenatide/insulin glargine was studied. However, due to the increased risk of hypoglycaemia, the SmPC for lixisenatide strongly recommends against this combination for safety reasons, please see further below. Information on both the not studied and studied OAD combinations is adequately reflected in sections 4.4 and 5.1 in the SmPC. However, due to the limitations in the available data, the indication has been restricted to the combination with metformin.

The data in patients switching from basal insulin alone is very limited. Although the outcome in this subgroup is comparable to that in the overall population, the data is not considered sufficient to support specific mentioning of this population in the indication especially when taking into account that this treatment regimen is not in accordance with standard of care.

There is a lack of long-term data beyond 30 weeks but further subgroup analyses of the patients reaching the maximum dose as well as data from the lixisenatide file have been provided. These data indicate that the effect can be maintained long-term for a majority of patients at the doses available.

Risks

Unfavourable effects

In the Phase 3 study pool there were no new or unexpected adverse events in any of the treatment groups. The most common treatment emergent adverse events reported as related to study drug (FRC) by the investigator were *nausea* (8.4%), *diarrhoea* (2.2%), *vomiting* (2.2%) and *dizziness* (1.4%). These four reactions are all labelled in the SmPC section 4.8 as "common".

The main difference in TEAE pattern between the treatment groups was that subjects on FRC compared to subjects on lixisenatide less often experienced gastrointestinal events (study EFC12404: *nausea*: 9.6% [FRC] vs 24.0% [lixisenatide] and *vomiting* 3.2%[FRC] vs 6.4% [lixisenatide]). The frequency of subjects experience diarrhoea was the same between subjects on FRC and lixisenatide (9%). On the other hand, subjects on FRC more often compared to subjects on insulin glargine experienced GI symptoms (*nausea:* 10.0% vs 2.3%; *diarrhoea*: 7.0% vs 3.6% and *vomiting*: 3.4% versus 1.1% for the FRC and insulin glargine groups, respectively in the Phase 3 study pool).

The percentages of patients with discontinuation of FRC due to GI event were low (0.7% due to nausea and 0.2% due to vomiting) and mostly the events were mild or moderate in severity and occurred with one or two episodes per patient.

The incidence of documented symptomatic hypoglycaemia was comparable between subjects on FRC compared to subjects on insulin glargine both in insulin naïve patients (25.6% [FRC] vs 23.6% [insulin glargine]) and patients earlier treated with insulin (40.0% [FRC] vs 42.5% [insulin glargine].

The FRC is provided in two different pens with two different ratios between insulin glargine and lixisenatide which may increase the risk for *medication errors*. The number of pen-related events per 100 PYE was in general slightly higher for subjects on FRC compared to both subjects on insulin glargine and lixisenatide, respectively. None of the-pen related events in any of the treatment groups was associated with a clinical event. *"Medication errors including mix-ups between the different strength of the product"* have been suggested as an important potential risk in the RMP and a warning regarding mix-ups between the 2 strength of Suliqua and other injectable diabetes medicinal product is reflected in the PIL and SmPC.

Adjudicated *allergic reactions* were reported in a low frequency (0.7%) of the subjects on FRC in the Phase 2/3 study pool. The PT:s of event judged as related to IMP (FRC) were all *urticaria.* The frequency of subjects reporting *injection site reactions* were seen in 1.7% of the subjects on FRC.

Development of antibodies against lixisenatide (ADA) occurred in approximately 36% of the subjects on FRC over 30 weeks of treatment. High concentrations of ADA have, in a small amount of subjects, shown a trend with decreased metabolic control (higher HbA1c) in clinical studies with lixisenatide (EFC11321). However, in the present study (EFC12404) most of the ADA positive subjects had low concentrations, below the lower limit of quantification (LLOQ).

In the population without prior treatment to insulin (study 12404), the rate of conversion from AIA negative status at baseline to positive status at Week 30, was higher in the FRC group (19%) compared with the insulin glargine group (9%). In patients earlier treated with basal insulin (study 12405) the increase was lower and

more similar between the treatment groups (FRC group15% in the FRC group vs 12% in the insulin glargine group). Frequency data regarding development of AIA against FRC and insulin differs between different studies. However, there is a consistency among the studies regarding in general low titres of AIA despite treatment group and no identified safety problems in relation to AIA positivity.

Uncertainty in the knowledge about the unfavourable effects

Experience and exposure of the two mono-components in Suliqua (insulin glargine and lixisenatide) is large and long-term safety data are available. There were no new or unexpected safety findings with the fixed combination of these products in the presented studies. However, knowledge about unfavourable effects could in many cases be extrapolated from knowledge from the two mono-components for example use in very elderly, use in subjects with moderate renal impairment, events of pancreatitis, pancreas cancer and cardiovascular safety.

The incidence of documented symptomatic hypoglycaemia was comparable between subjects on FRC compared to subjects on insulin glargine. However, the incidence of hypoglycaemic episodes will most probably increase when/if the FRC is co-administrated with SU. Therefore section 4.4 of the SmPC includes a warning against the combined use of FRC with SU.

"Medication errors including mix-ups between the different strength of the product" due to the two different pens with two different ratios between insulin glargine and lixisenatide with FRC may increase the risk for medication errors. This is reflected in the Product Information and as safety concern in the RMP (important potential risk). The applicant has proposed to conduct post-marketing cross-sectional surveys to evaluate the effectiveness of the additional risk minimization measures regarding medication error (i.e., Healthcare professional [HCP] and patient education materials).

Immunogenicity and development of neutralizing antibodies, especially in treatment of insulin naïve patients is an uncertainty. It is uncertain to rely on data from the two mono-components due to a potential risk of antibody formation against different epitopes (and different clinical effects) compared to the FRC. However, in the present studies no clinical relevance of presence of antibodies against either lixisenatide, insulin glargine or the FRC was noted. In clinical practice, the main plausible risk is that if neutralizing antibodies develop a dose adjustment is needed and this is reflected in the SmPC. In addition, *Immunogenicity/neutralization* is characterised as an important potential risk in the RMP.

Effects Table

Table 23 Effects Table for Suliqua in the treatment of T2DM (data cut-off: 25 Nov 2015).

Effect	Short Description	Unit	Suliqua	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
T2DM, Insulin naïve patients (Study EFC12404)						
HbA1c	Change in HbA1c from baseline	%	-1.63	-1.34 (insulin glargine)	Primary endpoint, treatment difference: -0.29 [-0.38 to -0.19]$_{95\%CI}$. Non-inferiority and superiority confirmed	Study EFC12404

Effect	Short Description	Unit	Suliqua	Control	Uncertainties / Strength of evidence	References
2-hour PPG excursion	Change in 2-hour PPG and plasma glucose excursion during a standardized meal test from baseline to Week 30	mmol/L	-2.31	-0.18 (insulin glargine)	Secondary endpoint, treatment difference of -2.13 [-2.50 to -1.77]$_{95\%CI}$. Superiority confirmed	Study EFC12404
Body weight	Change in body weight from baseline to Week 30	kg	-0.29	1.11 (insulin glargine)	Secondary endpoint, treatment difference of -1.40 [-1.89 to -0.91]$_{95\%CI}$. Superiority confirmed	Study EFC12404
HbA1c <7% with no body weight gain	Percentage of patients reaching HbA1c <7% with no body weight gain at Week 30	%	43.2	25.1 (insulin glargine)	Secondary endpoint, treatment difference of 18.08 [12.15 to 24.01]$_{95\%CI}$. Superiority confirmed	Study EFC12404
T2DM, Insulin treated patients (Study EFC12405)						
HbA1c	Change in HbA1c from baseline	%	-1.13	-0.62 (insulin glargine)	Primary endpoint, treatment difference: -0.52 [-0.63 to -0.40]$_{95\%CI}$. Superiority confirmed	Study EFC12405
2-hour PPG excursion	Change in 2-hour blood glucose excursion during a standardized meal test from baseline to Week 30	mmol/L	-3.90	-0.47 (insulin glargine)	Secondary endpoint, treatment difference of -3.43 [-3.92 to -2.94]$_{95\%CI}$. Superiority confirmed	Study EFC12405
Body weight	Change in body weight from baseline to Week 30	kg	-0.67	0.70 (insulin glargine)	Secondary endpoint, treatment difference of -1.37 [-1.81 to -0.93]$_{95\%CI}$. Superiority confirmed	Study EFC12405
HbA1c <7% with no body weight gain	Percentage of patients reaching HbA1c <7% with no body weight gain at Week 30	%	34.2	13.4 (insulin glargine)	Secondary endpoint, treatment difference of 20.8 [15.0 to 26.7]$_{95\%CI}$. Superiority confirmed	Study EFC12405
Unfavourable Effects						
Gastro-intestinal events	Reported AEs on a SOC level	%	19.7* 21.7**	10.6*(insulin glargine) 36.9** (lixisenatide)		*Phase 3 study pool ** Study EFC12404

Effect	Short Description	Unit	Suliqua	Control	Uncertainties/ Strength of evidence	References
Nausea	Reported AEs PT level	%	10* 9.6**	3.3* (insulin glargine) 24.0** (lixisenatide)		*Phase 3 study pool ** Study EFC12404
Vomiting	Reported AEs PT level	%	3.4* 3.2**	1.1*(insulin glargine) 6.4** (lixisenatide)		*Phase 3 study pool ** Study EFC12404
Diarrhoea	Reported AEs PT level	%	7.0* 9.0**	3.6* (insulin glargine) 9.0** (lixisenatide)		*Phase 3 study pool ** Study EFC12404
Documented symptomatic Hypoglycaemia (insulin naïve patients)	plasma glucose ≤3.9 mmol/L [70 mg/dL])	Number of events per patient year (%)	1.44 (25.6)	1.22 (23.6) Insulin glargine 0.34 (6.4%) lixisenatide		Study EFC12404
Hypoglycaemia (patients earlier treated with insulin)	plasma glucose ≤3.9 mmol/L [70 mg/dL])	Number of events per patient year (%)	3.03 (40.0)	4.22 (42.5)		Study EFC12405
Allergic reactions	Reported AEs	%	0.7* 1.3**	0.5*(insulin glargine) 0.9** (lixisenatide)		*Phase 2/3 study pool ** Study EFC12404
Injection site reactions	Reported AEs	%	1.7* 2.6**	1.1* (insulin glargine) 3.0%** (lixisenatide)		*Phase 2/3 study pool ** Study EFC12404
Anti-lixisenatide antibodies (ADA)	Conversion rate of ADA negative at baseline to ADA positive after 30 weeks	%	36	48 (lixisenatide)		Study EFC12404
Anti-insulin antibodies (AIA)	Conversion rate of AIA negative at baseline to AIA positive after 30 weeks	%	18.1	8.9 (insulin glargine)		Study EFC12404(insulin naïve)
Anti-insulin antibodies (AIA)	Conversion rate of AIA negative at baseline to AIA positive after 30 weeks	%	14.7	11.5 (insulin glargine)		Study EFC12405(prior treatment with basal insulin)

Abbreviations: T2DM=Type 2 diabetes mellitus

Balance

Importance of favourable and unfavourable effects

Metabolic control in terms of normalising HbA1c is challenging in the T2DM population when metformin monotherapy no longer is enough to achieve treatment goals. Therefore, the availability of several treatment options is needed to facilitate an individualized treatment strategy. Concomitant treatment with basal insulin and a GLP-1 RA can be an important treatment option for patients who are eligible for initiation of insulin treatment as well as those in need of intensified insulin treatment. The benefits compared to insulin monotherapy include a superior reduction of HbA1c combined with weight stability and a comparable or lower risk of hypoglycaemia due to the fact that the insulin doses can be kept at a lower level compared to what would be needed to reach the same HbA1c level with insulin only. The disadvantages include the risks associated with GLP-1 RA use, mainly GI adverse events. However, such events are in the majority of the cases transient.

Suliqua has been shown to be efficient in lowering HbA1c, both in insulin naïve patients and in patients switched from a basal insulin therapy. The effect was superior to that of both mono-components although the treatment difference when compared to insulin glargine could be considered to be of borderline clinical relevance as the lixisenatide component contributes less to the glucose-lowering effect of the FRC than the insulin glargine component. However, the data do show that both components significantly contribute to the effect, with insulin glargine primarily affecting the overall glucose level as reflected by a decrease in fasting plasma glucose while lixisenatide primarily lowers the post-prandial glucose excursions. Compared to insulin glargine, a greater effect on HbA1c was achieved without weight gain and at a comparable rate of hypoglycaemias. A similar degree of reduction of HbA1c could theoretically have been achieved with a higher insulin dose, but this would most likely have resulted in additional weight increase and a higher incidence of hypoglycaemia.

Co-administration of two injectable medicinal products in one injection is convenient and could possibly increase compliance. This advantage should be weighed against the somewhat complicated regimen, which in most cases necessitates a change from Pen A to Pen B over time.

The safety profile of the FRC (fixed-ratio combination insulin glargine/lixisenatide) is in general similar to the two included mono-components with no indications of additive toxicity. The incidence of GI adverse events is lower compared to lixisenatide given as monotherapy. This can be an advantage even though GI adverse events diminish over time.

In the present Phase 2/3 studies for FRC there were no cases of pancreatitis or increased heart rate of clinical importance noted in the FRC group. However, these are unfavourable effects that have been noted for GLP1 RA in general (class effects) and thus are putative risks also for the FRC even if this was not demonstrated in the presented Phase 2/3 studies.

Benefit-risk balance

The benefits of achieving a superior reduction of HbA1c with Suliqua compared to the mono-components in combination with weight stability and most likely a lower incidence of hypoglycaemias compared to what would be the result of the higher insulin dose needed to reach the same HbA1c target, is considered to outweigh the additional risks which mainly included transient GI adverse events. The main target population for Suliqua is expected to be patients eligible for initiation or intensification of insulin treatment and where there is a need to avoid (further) weight increase.

Suliqua was only studied in combination with metformin in the pivotal studies. Further to this, the only external support for the triple combination with other OADs comes from the lixisenatide file where the triple combination SU/lixisenatide/insulin glargine was studied.

However, due to the increased risk of hypoglycaemia, the SmPC for lixisenatide includes a warning against the combination for safety reasons. Due to the limitations in the available data, the indication has been restricted to the combination with metformin.

Furthermore, the data in patients switched from basal insulin alone is considered insufficient to allow inclusion of this population in the indication, also taking into account that this treatment regimen is not in accordance with standard of care. Therefore the target population is restricted to patients failing on oral glucose-lowering products alone or combined with basal insulin.

3.1. Conclusions

The overall B/R of Suliqua is 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 Suliqua is favourable in the following indication:

Suliqua is indicated in combination with metformin for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin (see section 4.4 and 5.1 for available data on the different combinations).

The CHMP 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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

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 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.

Additional risk minimisation measures

Prior to launch of Suliqua in each Member State, the Marketing Authorisation Holder (MAH) must agree the content and format of the educational materials for Suliqua, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational materials are aimed at ***increasing awareness about the two available strengths of the product*** *and at* ***minimising the risk of medication errors including mix-ups between the different strengths of the product****.*

The MAH shall ensure that, in each Member State where Suliqua is marketed, all healthcare professionals who are expected to prescribe, dispense and patients who are expected to use Suliqua, have access to/are provided with the following educational package:

- *Healthcare Professional Guide;*
- *Patient Guide.*

The Healthcare Professional Guide shall contain the following key messages:

- *Provide patients with the patient guide prior to prescribing or dispensing Suliqua.*
- *Ensure that your patients and their caretakers are adequately informed on how to use insulin glargine/lixisenatide.*
- *Suliqua is supplied in a pre-filled pen and must only be used with this device; healthcare professionals must never use a syringe to withdraw insulin glargine/lixisenatide from a pre filled pen or dosing errors and serious harm can result.*
- *Suliqua is available in two pre filled pens containing different strengths of lixisenatide, and different dose ranges:*
  - *Both pre filled pens contain insulin glargine in a strength of 100 units/mL*
  - *Suliqua 10-40 pen allows daily doses between 10 and 40 dose steps of Suliqua to be given (strength: insulin glargine 100 units/mL and lixisenatide 50 mcg/mL; dose range: 10 to 40 units of insulin glargine in combination with 5 to 20 mcg lixisenatide)*
  - *Suliqua 30-60 pen allows daily doses between 30 and 60 dose steps of Suliqua to be given (strength: insulin glargine 100 units/mL and lixisenatide 33 mcg/mL; dose range: 30 to 60 units insulin glargine in combination with 10 to 20 mcg lixisenatide)*
- *The prescription must state the dose range and strength of the Suliqua pre filled pen and the number of dose steps to be administered.*
- *The Pharmacist should clarify with the prescriber any incomplete prescription.*
- *Explain to your patient that:*
  - *You are prescribing a number of dose steps which corresponds to a set number of units of insulin plus a fixed amount lixisenatide*

    - *For Suliqua, one dose step always contains one unit of insulin, regardless of the Suliqua pre filled pen being used (10-40 pen or 30 60 pen)*
    - *The dose counter of the pen device shows the number of dose steps to be injected,*
- *If the patient has been transferred from a different pre filled pen device, highlight the differences in design between the two devices (focus on colour differentiation, warning statements on carton/label and other safety design features such as tactile elements on the prefilled pen).*
- *Explain what the patient should anticipate regarding dysglycemia and potential adverse reactions.*
- *Pharmacists are encouraged to check that patients and caretakers are able to read the strength of Suliqua, the dose range of the pre filled pen and the dose counter of the pre filled pen before dispensing insulin glargine/lixisenatide. Pharmacists should also check that patients have been trained on how to use the pen.*
- *Patients who are blind or with poor vision must be instructed to always get assistance from another person who has good vision and is trained in using insulin glargine/lixisenatide pen device.*
- *Tell patients to closely monitor their blood sugar levels when starting insulin glargine/lixisenatide which contains insulin glargine and a non-insulin active substance (lixisenatide).*
- *A reminder on the need to report all medication errors with Suliqua will be part of the healthcare professional guide.*

The Patient Guide shall contain the following key messages:

- *Read the instructions in your package leaflet carefully before using Suliqua.*
- *Suliqua is supplied in a pre-filled pen and must only be used with this device; patients, carers and healthcare professionals must never use a syringe to withdraw insulin glargine/lixisenatide from a pre-filled pen or dosing errors and serious harm can result.*
- *Suliqua is available in two pre-filled pens containing two different strengths of lixisenatide, and different dose ranges:*
    - *Both pre-filled pens contain insulin glargine in a strength of 100 units/mL*
    - *Suliqua 10-40 pen allows daily doses between 10 and 40 dose steps of Suliqua to be given (strength: insulin glargine 100 units/mL and lixisenatide 50 mcg/mL; dose range: 10 to 40 units of insulin glargine in combination with 5 to 20 mcg lixisenatide)*
    - *Suliqua 30-60 pen allows daily doses between 30 and 60 dose steps of Suliqua to be given (strength: insulin glargine 100 units/mL and lixisenatide 33 mcg/mL; dose range: 30 to 60 units insulin glargine in combination with 10 to 20 mcg lixisenatide)*
- *The prescription should mention the pre-filled pen type you need (Suliqua 10-40 pen or 30-60 pen) and the number of dose steps to be injected.*
- *The Pharmacist should clarify with the prescriber any incomplete prescription.*
- *One dose step contains one unit of insulin glargine plus a fixed amount of lixisenatide. Before you use insulin glargine/lixisenatide, be clear on how many dose steps you require. Your healthcare professional will give you this information.*
- *For Suliqua, one dose step always contains one unit of insulin, regardless of the Suliqua pre-filled pen being used (10-40 pen or 30-60 pen).*
- *Your healthcare professional will explain the design and features of your Suliqua pen, including how the dose counter of the pre-filled pen device shows the number of dose steps to be injected.*
- *During the switch to this type of combination medicine and in the weeks after the switch you should measure your blood sugar levels more frequently.*
- *If you have any questions about your treatment speak to your healthcare professional.*
- *A reminder on the need to report all medication errors with Suliqua will be part of patient guide.*

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable