30 January 2020
EMA/CHMP/82348/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

SULIQUA

International non-proprietary name: insulin glargine / lixisenatide

Procedure No. EMEA/H/C/004243/II/0011

Note

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

Table of contents

List of abbreviations

ADA/EASD:	American Diabetes Association/European Association for the Study of Diabetes
AE:	adverse event
AIA:	anti-insulin antibody
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
ARAC:	Allergic Reaction Assessment Committee
BID:	twice daily
CI:	confidence interval
CT:	computed tomography
EU:	European Union
FPG:	fasting plasma glucose
FRC:	insulin glargine/lixisenatide fixed-ratio combination
GLP-1 RA:	glucagon-like peptide-1 receptor agonist
HbA1c:	glycated haemoglobin
LS:	least squares
mITT:	modified intent-to-treat
MMRM:	mixed-effect model with repeated measures
OAD:	oral anti-diabetic drug
PBRER:	Periodic Benefit-Risk evaluation Report
PK:	pharmacokinetics
PPG:	postprandial plasma glucose
PSAC:	Pancreatic Safety Assessment Committee
PT:	preferred term
QD:	once daily
QW:	once weekly
SAE:	serious adverse event
SGLT2:	sodium-glucose cotransporter 2
SMPG:	self-monitored plasma glucose
SOC:	system organ class
T1DM:	Type 1 diabetes mellitus
T2DM:	Type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
TSI:	Tracked Safety Issue
ULN:	upper limit of the normal
US:	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, sanofi-aventis groupe submitted to the European Medicines Agency on 12 March 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to include "treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to other oral medicinal products for the treatment of diabetes" based on the phase 3 Study EFC13794; a 26-week randomized, open-label, active controlled, parallel-group, study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with Type 2 Diabetes inadequately controlled on GLP-1 receptor agonist and metformin (alone or with pioglitazone and/or SGLT-2 inhibitors), followed by a fixed ratio combination single-arm 26-week extension period.

As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the contact details of the local representatives in Denmark, the Netherlands and the UK in the Package Leaflet and to implement minor editorial changes in the annexes. An updated RMP version 4.0 was provided as part of the application.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 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 MAH 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 MAH did not seek Scientific Advice at the CHMP.

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: N/A

Timetable	Actual dates
Submission date	12 March 2019
Start of procedure	30 March 2019
CHMP Rapporteur Assessment Report	23 May 2019
PRAC Rapporteur Assessment Report	29 May 2019
PRAC members comments	5 June 2019
Updated PRAC Rapporteur Assessment Report	6 June 2019
PRAC Outcome	14 June 2019
CHMP members comments	18 June 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 June 2019
1st Request for supplementary information (RSI) and extension of timetable adopted by the CHMP on	27 June 2019
MAH's responses submitted to the CHMP on	15 August 2019
CHMP Rapporteur response Assessment Report	18 September 2019
PRAC Rapporteur response Assessment Report	19 September 2019
PRAC Outcome	3 October 2019
CHMP members comments	9 October 2019
Updated joint Rapporteur response Assessment Report	10 October 2019
2nd Request for supplementary information (RSI) and extension of timetable adopted by the CHMP on	17 October 2019
MAH's responses submitted to the CHMP on	4 December 2019
CHMP Rapporteur response Assessment Report	7 January 2020
CHMP members comments	22 January 2020
Updated joint Rapporteur response Assessment Report	24 January 2020
CHMP Opinion	30 January 2020

2. Scientific discussion

2.1. Introduction

Suliqua (insulin glargine/lixisenatide) is the fixed ratio combination of the long-acting human insulin analogue insulin glargine U100 with the glucagon-like peptide-1 receptor agonist (GLP-1 RA) lixisenatide.

Insulin glargine, a recombinant analogue of human insulin providing a 24-hour basal insulin supply after a single-dose subcutaneous (SC) injection. Insulin glargine U100 has been marketed as Lantus for approximately 18 years.

Lixisenatide, a primarily postprandial-acting GLP-1 RA, has been approved since 2013 as Lyxumia in the European Union (EU). Lixisenatide is currently approved in over 70 countries worldwide.

The fixed ratio combination of insulin glargine U100 and lixisenatide (hereafter referred to as FRC) administered as a once daily (QD) injection has been developed for the treatment of patients with type 2 diabetes mellitus (T2DM) not adequately controlled on oral anti-diabetic drug (OAD) and/or basal insulin. In contrast to a fixed-dose combination, the concept of the FRC allows both insulin glargine titration to fasting glucose targets and concomitant slow dose increase of lixisenatide.

The FRC was approved in the EU in January 2017, under the trade name of Suliqua in combination with metformin for the treatment of adults with T2DM 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.

In the current application, the MAH proposed to update the product information, based on the results of the first 26-week (randomized, open-label, active-controlled) period of the Phase 3b EFC13794 (LixiLan-G) study. This study was designed to evaluate the efficacy and safety of the FRC in patients with T2DM not sufficiently controlled on OAD therapy (metformin ± pioglitazone ± sodium-glucose co-transporter 2 [SGLT-2] inhibitor treatments) and GLP-1 RA therapy (liraglutide, exenatide, exenatide extended-release, albiglutide, and dulaglutide). This population was not studied during the Phase 3 program.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

The current application is based on the results of one study, HOE901/AVE0010-EFC13794, hereafter referred to as Study EFC13794.

GCP

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

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

2.4. Clinical efficacy

2.4.1. Main study

Study EFC13794

This was a 26-week randomized, open-label, active controlled, parallel-group study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with Type 2 Diabetes inadequately controlled on GLP-1 receptor agonist and metformin (alone or with pioglitazone and/or SGLT-2 inhibitors), followed by a fixed ratio combination single-arm 26-week extension period (LixiLan-G).

Methods

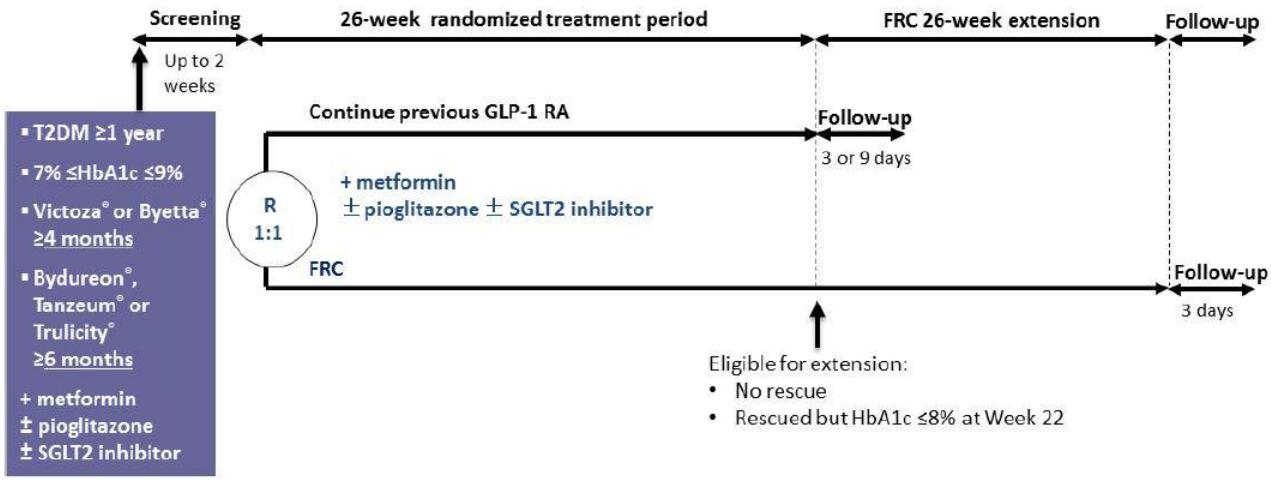
The study was designed as an open-label, 1:1 randomized, active-controlled, 2-arm, 26-week treatment duration, parallel group multinational and multicenter Phase 3b study comparing:

- Insulin glargine/lixisenatide fixed ratio combination (FRC) group;
- Glucagon-like peptide-1 (GLP-1) receptor agonist group.

At the end of the 26-week randomized treatment period, patients from the FRC group were invited to participate in a 26-week single arm extension period (data not reviewed in the current application).

The study comprised 4 periods (see **Figure 1**): (1) an up-to 2-week screening period; (2) a 26-week open-label randomized treatment period; (3) a 26-week single-arm extension period and (4) a post treatment safety follow-up period (patients who prematurely discontinue the study treatment will continue in the study up to the scheduled date of study completion).

Figure 1 – Study design



Abbreviations: GLP-1 RA: glucagon-like peptide-1 receptor agonist, FRC: fixed-ratio combination of insulin glargine and lixisenatide, HbA1c: glycated hemoglobin, R: randomization, SGLT2: sodium-glucose cotransporter 2, T2DM: type 2 diabetes mellitus

Study participants

The study recruited outpatients with T2DM diagnosed at least one year prior to screening and who have been treated with a once/twice daily (QD/BID) GLP-1 RA (liraglutide, exenatide) for at least 4 months (at stable dose for at least 3 months) or a weekly GLP-1RA (exenatide extended-release, albiglutide, dulaglutide) for at least 6 months at a stable dose corresponding to the maximal tolerated dose, in combination with metformin with or without pioglitazone and/or a SGLT-2 inhibitor prior to screening. Key inclusion and exclusion criteria are shown in **Table 1**.

Table 1 - Key inclusion and exclusion criteria – Study EFC13794

Inclusion criteria
- T2DM diagnosed at least one year prior to screening visit - Current treatment with GLP-1 RAs for at least 4 months (Liraglutide, Exenatide) or 6 months (Exenatide extended-release, Albiglutide or Dulaglutide) in combination with metformin ± pioglitazone ± SGLT-2 inhibitor
Exclusion criteria
- HbA1c <7% (53 mmol/mol) and >9% (75 mmol/mol) - Body mass index (BMI) ≤20 or >40 kg/m² - Use of anti-diabetic drugs within 3 months prior to screening visit other than those described in inclusion criteria - Previous treatment with insulin in the year prior to screening visit (except for short-term treatment due to intercurrent illness including gestational diabetes) - History of hypoglycaemia unawareness - History of metabolic acidosis, including diabetic ketoacidosis within 1 year prior to screening visit - Personal or immediate family history of medullary thyroid cancer (MTC) or genetic conditions that predispose to MTC (eg, multiple endocrine neoplasia type 2 syndromes) - History of stroke, myocardial infarction, unstable angina, or heart failure requiring hospitalization within the last 6 months prior to screening visit. - Calcitonin ≥20 pg/mL (5.9 pmol/L) at screening

Treatments

Patients received study treatment with FRC or unchanged GLP-1 RA, both on top of previous OAD therapy (metformin ± pioglitazone ± SGLT-2 inhibitors) at stable doses. The dose of the FRC was titrated according to the patient's need for insulin glargine. There were two pens with different insulin glargine/lixisenatide fixed ratios, which allowed insulin glargine titration from 10 to 60 U while limiting lixisenatide dose to a maximum of 20 µg/day:

- Peach Pen: pre-filled disposable SoloStar pen-injector containing 3 mL of sterile solution of 100 U/mL insulin glargine and 50 µg/mL lixisenatide in ratio of 2:1 (2 units of insulin glargine per 1 µg lixisenatide);

- Olive Pen: pre-filled disposable SoloStar pen-injector containing 3 mL of sterile solution of 100 U/mL insulin glargine and 33 µg/mL lixisenatide in ratio of 3:1 (3 units of insulin glargine per 1 µg lixisenatide).

Initial daily dose of FRC to be administered was 10 U (10 U insulin glargine / 5 µg lixisenatide). During the first 8 weeks of treatment, the dose was to be titrated twice a week based on the insulin glargine dose, until the patient reached a target fasting SMPG of 4.4 to 5.6 mmol/L (80 to 100 mg/dL) while avoiding hypoglycaemia episodes. Thereafter, from Week 8 until Week 26, the dose in units was to be adjusted as necessary to maintain this fasting SMPG target.

The total daily dose of FRC was capped at 60 U. If glucose parameters exceeded the threshold value defined for rescue therapy at the maximum defined daily dose of 60 U, the FRC dose was maintained at 60 U and a rescue therapy was added.

Choice of comparator

In the comparison/reference product arm, GLP-1 RAs were administered as per local labelling at the same dose schedule as prior to randomization. Per protocol, the dose of GLP-1 RA at screening had to be the highest dose approved unless not tolerated according to Investigator's judgment as documented in the patient's medical file. The GLP-1 RA dose was to be kept stable during the study.

Non-IMP background therapy (metformin ≥1500 mg/day with or without pioglitazone and/or a SGLT-2 inhibitor, all at stable doses for at least 3 months) was administered according to the respective local product labelling at a stable dose (unchanged versus screening) throughout the study unless there was a safety issue related to this treatment.

Rescue therapy could be given for refractory hyperglycaemia, either as rapid acting insulin for patients in the FRC arm who already reached the maximal daily dose of 60 U or as basal insulin for patients in the GLP-1 RA arm.

Objectives

The primary objective of Study EFC13794 was to demonstrate the superiority of the insulin glargine/lixisenatide FRC versus GLP-1 RA in HbA1c change from baseline to Week 26.

The secondary objectives of the study were: percentage of patients reaching HbA1c targets, FPG, 7-point SMPG profile, glycaemic control after a standardized meal test, body weight and safety and tolerability.

Other objectives included: insulin glargine and lixisenatide doses in the combination group, development of anti-insulin antibodies (FRC group), development of anti- lixisenatide antibodies (FRC group) and total plasma concentration of lixisenatide before and following injection (FRC group).

Outcomes/endpoints

The primary efficacy endpoint was the change in HbA1c (%) from baseline to Week 26.

Secondary endpoints included continuous and categorical endpoints, as follows:

- Continuous secondary efficacy endpoints
    - Change in FPG from baseline to Week 26
    - Change in 7-point SMPG profiles from baseline to Week 26 (each time point and average daily value)

- Change in 2-hour PPG and in blood glucose excursion during standardized meal test from baseline to Week 26
- Change in body weight from baseline to Week 26

- Categorical secondary efficacy endpoints
  - Percentage of patients reaching HbA1c ≤6.5% (48 mmol/mol) at Week 26
  - Percentage of patients reaching HbA1c <7% (53 mmol/mol) at Week 26
  - Percentage of patients requiring rescue therapy during the 26 weeks treatment period
- Other exploratory endpoints:
  - Insulin glargine and lixisenatide doses at Week 26 in the FRC group
  - C-peptide evaluation during standardized meal test from baseline to Week 26
  - Percentage of patients reaching HbA1c <7% (53 mmol/mol) with no body weight gain from baseline to Week 26
  - Percentage of patients reaching the fasting SMPG target (≤100 mg/dL) at Week 26 in the FRC group
  - Percentage of patients with no weight gain at Week 26

Sample size

The sample size calculations are based on the primary efficacy variable change in HbA1c from baseline to Week 26 and ITT analysis, with the following assumptions:

- A common standard deviation of 1.1%
- A 0.4% mean difference between FRC and GLP-1 receptor agonist in change in HbA1c from baseline to Week 26
- A drop-out rate of 20%. The patients in the FRC group who discontinued treatment are assumed to respond the same as the control patients, i.e., no treatment difference between the patients in the FRC group who discontinued treatment and the control patients.
- A t-test at a 2-sided 5% significance level with at least 90% power.

Based on the above assumptions, 500 patients (250 per group) were needed for this study.

Randomisation

At the end of screening period, eligible patients were centrally randomized (using permuted block randomization schedule) via IRT in a 1:1 ratio to 1 of the 2 treatment groups. The patients were stratified by value of HbA1c at screening (<8%, ≥8%) and GLP-1 receptor agonist subtype at screening (once (QD)/twice daily (BID) formulations, once weekly (QW) formulations).

The study was designed as open-label because of differences in the type and number of pens used to administer the FRC and the various GLP-1 RAs in the comparator arm.

Blinding (masking)

This study had an open-label design. To compensate for lack of blinding, the Investigator and the Sponsor did not have access to the data of the primary efficacy endpoint (i.e., HbA1c) nor to the data of the standardized meal test endpoints obtained after baseline visit until the end of the 26-week randomized comparative study period. The Sponsor's study team could review the data for the primary efficacy parameter in descriptive statistics with the name of the IMP treatment masked during data review meetings.

Statistical methods

Efficacy analysis

The efficacy analysis was based on the modified Intent-to-treat (mITT) population using efficacy assessment collected during the study, including those obtained after investigational medicinal product (IMP) discontinuation or introduction of rescue therapy. The mITT population consisted of all randomized patients who had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.

Primary efficacy endpoint analysis – primary analysis:

The primary efficacy endpoint was analysed using a mixed-effect model with repeated measures MMRM) under the missing at random framework. The MMRM model included treatment group (FRC or GLP-1 RA), randomization strata of HbA1c (<8%, ≥8%) at V1 (Week -2), randomization strata of GLP-1 RA subtype (once/BID formulations, QW formulations) at screening, visit (Week 8, Week 12, Week 18, Week 22 and Week 26), treatment by-visit interaction and world region as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. The adjusted mean change in HbA1c from baseline to Week 26 for each treatment group was estimated in the framework of this model, as well as the between group difference in least square (LS) means and the corresponding 95% confidence interval (CI). The statistical test was 2-sided at the significance level of 5%. The primary efficacy endpoint was also analysed by various sensitivity analyses including the ANCOVA with missing data at Week 26 imputed with respect to jump to control under missing not at random assumption.

Sensitivity analyses of the primary efficacy endpoint

The following sensitivity analyses were performed for the primary endpoint:

- The same MMRM model as described in the primary analysis including only the scheduled HbA1c measurements collected during the 26-week on-treatment period.
- The same MMRM model on the 26-week completers in the mITT population (ie, all mITT patients who completed the 26-week open-label randomized treatment period and did not start any rescue therapy before the end of the 26-week randomized treatment period) using the observed Week 26 values and the same MMRM model as described above.
- The same MMRM model as described in the primary analysis excluding the measurements after receiving the rescue therapy.
- An analysis of covariance (ANCOVA) using multiple imputations with respect to jump to control under the missing not at random assumption.

Secondary efficacy endpoint analysis:

Except for 2-hour PPG and glucose excursion, all continuous secondary efficacy endpoints were analysed using the same MMRM approach with the corresponding baseline value-by-visit interaction as a covariate

to compare FRC with GLP-1 RA. Differences between treatment groups and CI were estimated within the framework of MMRM.

2-hour PPG and glucose excursion (for each of which only 1 post-baseline assessment was scheduled) were analysed using analysis of covariance (ANCOVA) with the missing data at Week 26 imputed by LOCF to compare FRC with GLP-1 RA.

All categorical secondary efficacy endpoints defined were analysed by a Cochran-Mantel-Haenszel method stratified by the randomization strata. The proportion in each treatment group was provided, as well as the differences in proportions between groups with associated 2-sided 95% CIs.

A step-down testing procedure was applied in order to control the type 1 error. Once the primary endpoint was statistically significant at the 5% 2-sided level, testing was performed according to the following order: percentage of patients reaching HbA1c < 7% at Week 26, FPG, average 7-point SMPG, 2-hour PPG and/or glucose excursion. When an endpoint was not statistically significant at the 5% level, subsequent tests were not performed.

Additional efficacy analyses:

Analyses of other efficacy endpoints were descriptive, and no statistical test was performed.

Safety analysis

The safety analysis was descriptively performed, based on the safety population, defined as all randomized patients who received at least one dose of open-label IMP, regardless of the amount of treatment administered. Patients were analysed according to the treatment actually received (as treated).

Results

Participant flow

Subject disposition is shown in ***Figure 2***. Of the 840 patients screened, 514 were randomized (257 patients in the FRC group and 257 in the GLP-1 RA group) in 112 sites across 9 countries. Of these, 3 patients (2 in the FRC group and 1 in the GLP-1 RA group) were randomized but not treated, all of them per subject's request and due to "other" reasons. The main reason for screen failures was HbA1c outside range at screening visit (198 patients [23.6% of screened patients]).

Most of the patients completed the 26-week randomized treatment period (89.5% in the FRC group and 95.7% in the GLP-1 RA group).

The percentage of patients who permanently discontinued IMP during the 26-week randomized treatment period was low in both groups and higher in the FRC group (25 patients [9.7%]) than in the GLP-1 RA group (10 patients [3.9%]). The main reasons for IMP discontinuation were other reasons and AEs in the FRC group (4.7% and 3.9% respectively) and other reasons in the GLP-1 RA group (3.9%) (***Table 2***). Of note, other reasons did not include any safety-related findings.

Figure 2 - Patient disposition for the 26-week randomized treatment period

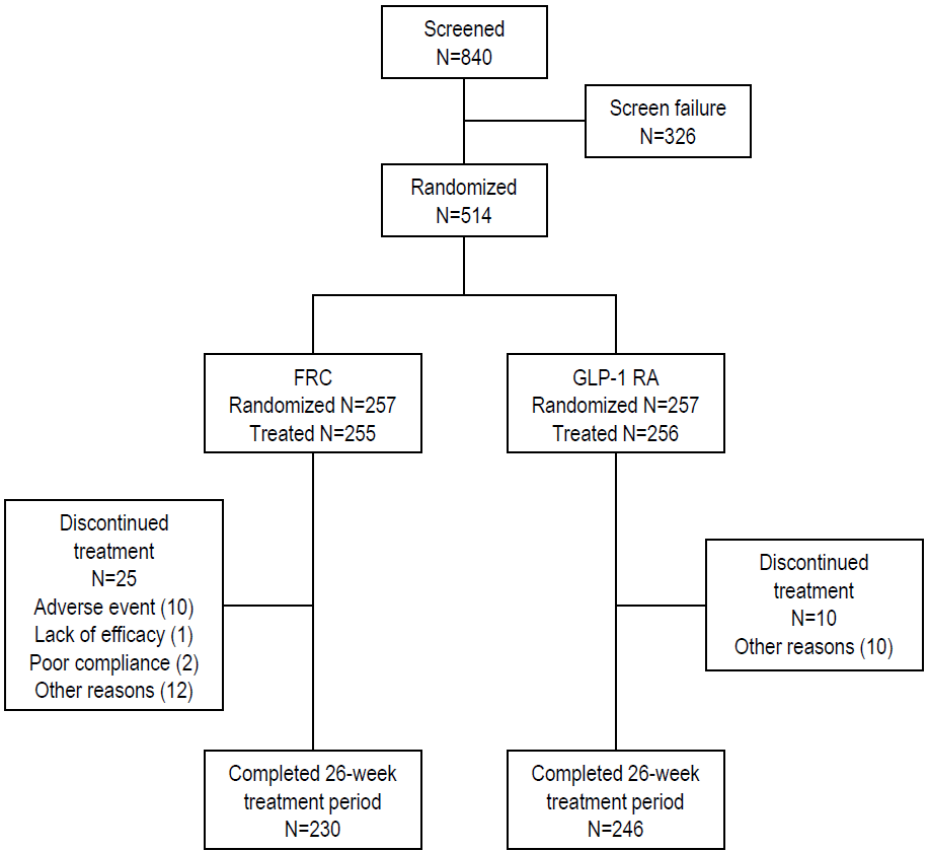


Table 2 - Patient disposition for the 26-week randomized treatment period

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)
Randomized and not treated	2 (0.8%)	1 (0.4%)
Subject's request for not treated	2 (0.8%)	1 (0.4%)
Reason for not treated		
Adverse event	0	0
Hypoglycemia	0	0
Lack of efficacy	0	0
Poor compliance to protocol	0	0
Other	2 (0.8%)	1 (0.4%)
Randomized and treated	255 (99.2%)	256 (99.6%)
Completed the 26-week randomized study treatment	230 (89.5%)	246 (95.7%)
Did not complete the 26-week randomized study treatment	25 (9.7%)	10 (3.9%)
Subject's request for treatment discontinuation during the 26-week randomized treatment period	14 (5.4%)	8 (3.1%)
Reason for study treatment discontinuation		
Adverse event	10 (3.9%)	0
Hypoglycemia	0	0
Lack of efficacy	1 (0.4%)	0
Poor compliance to protocol	2 (0.8%)	0
Other	12 (4.7%)	10 (3.9%)
Status at last study contact of patients who permanently discontinued the treatment during the 26-week randomized treatment period		
Alive	27 (10.5%)	11 (4.3%)
Dead	0	0

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

Recruitment

Patients from 9 participating countries were enrolled (Canada, Estonia, Germany, Israel, Romania, Slovakia, Spain, Italy, and the United States). Of the 124 centres that conducted screening, patients were randomized in 112 sites.

The study was initiated on 06 July 2016 and completed on 25 May 2018

Conduct of the study

Protocol deviations

The number of critical or major automatic protocol deviations (i.e., deviations identified from the database based on preconfigured rules) was small and balanced across treatment groups, with no apparent distribution pattern (12 [4,7%] in the FRC group vs 8 [3,1%] in the GLP1-RA group). Accordingly, these

were unlikely to have any impact on the overall outcome of the study. The most frequent category of major or critical automatic deviations in the FRC group was IMP administered but not as per protocol.

Amendments

Two amendments were made to the original protocol. In September 2016, a single-arm FRC 26-week extension period was introduced to provide additional assessment of all safety, efficacy and other endpoints over 52 weeks in total. Additionally, pharmacokinetic and antibody assessments were added in the FRC treatment group to gain information about exposure to lixisenatide and to assess the immunogenicity of insulin glargine and lixisenatide. In May 2017, inclusion of patients receiving background treatment of SGLT-2 inhibitors was allowed.

Baseline data

The demographics (***Table 3***) and patient (***Table 4***) baseline characteristics were well balanced between treatment groups. The median age of patients was 60.0 years and the majority of patients were white (94.4%), and males (52.5%). The mean BMI of patients at baseline was about 33 kg/m^2, and approximately 73% of the patients had a BMI value ≥30 kg/m^2, indicating that most patients were obese.

The diabetic history and disease characteristics at baseline (***Table 5***) were generally comparable between the treatment groups and so did the rate of diabetes microvascular complications. The mean diabetes duration was approximately 11 years.

All patients were on maximal tolerated dose of GLP-1 RA at screening as well as metformin (as per inclusion criteria). The mean daily dose at baseline was similar between the treatment groups. Overall, 16.3% of patients were receiving another OAD at screening: SGLT-2 inhibitors (10.1%) and/or pioglitazone (6.6%).

Table 3 - Key demographics at baseline

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
Age (years)			
Number	257	257	514
Mean (SD)	59.2 (9.6)	60.0 (10.3)	59.6 (10.0)
Median	59.0	60.0	60.0
Min : Max	30 : 82	25 : 84	25 : 84
Age group (years) [n (%)]			
Number	257	257	514
< 50	37 (14.4%)	40 (15.6%)	77 (15.0%)
≥ 50 - <65	130 (50.6%)	127 (49.4%)	257 (50.0%)
≥ 65 - <75	84 (32.7%)	75 (29.2%)	159 (30.9%)
≥ 75	6 (2.3%)	15 (5.8%)	21 (4.1%)
Gender [n (%)]			
Number	257	257	514
Male	126 (49.0%)	144 (56.0%)	270 (52.5%)
Female	131 (51.0%)	113 (44.0%)	244 (47.5%)

Table 4 - Patient characteristics baseline

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
HbA1c (%) at Visit 1 (Week -2)			
Number	257	257	514
Mean (SD)	7.86 (0.56)	7.88 (0.53)	7.87 (0.54)
Median	7.80	7.90	7.80
Min : Max	7.0 : 9.0	7.0 : 9.0	7.0 : 9.0
Randomization strata of Hba1c (%) at Visit 1 (Week -2) [n (%)]			
Number	257	257	514
<8	149 (58.0%)	147 (57.2%)	296 (57.6%)
≥8	108 (42.0%)	110 (42.8%)	218 (42.4%)
Randomization strata of GLP-1 receptor agonist subtype at screening [n (%)]			
Number	257	257	514
Once/twice daily formulation	153 (59.5%)	154 (59.9%)	307 (59.7%)
Once weekly formulation	104 (40.5%)	103 (40.1%)	207 (40.3%)
Baseline BMI (kg/m^2)			
Number	257	257	514
Mean (SD)	32.79 (4.40)	32.95 (4.38)	32.87 (4.38)
Median	32.90	33.00	32.90
Min : Max	21.2 : 40.0	21.5 : 40.0	21.2 : 40.0
Baseline BMI categories (kg/m^2) [n (%)]			
Number	257	257	514
< 30	71 (27.6%)	69 (26.8%)	140 (27.2%)
≥ 30	186 (72.4%)	188 (73.2%)	374 (72.8%)

BMI = Body Mass Index.

a Includes patients with more than one race, unknown or not reported

Table 5 - Disease characteristics at baseline

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
Duration of diabetes (years)			
Number	257	257	514
Mean (SD)	11.23 (7.42)	10.95 (6.08)	11.09 (6.78)
Median	10.05	9.83	9.99
Min : Max	1.0 : 57.9	1.4 : 40.1	1.0 : 57.9
Age at onset of Type 2 diabetes (years)			
Number	257	257	514
Mean (SD)	47.9 (10.0)	49.0 (9.2)	48.5 (9.6)
Median	50.0	50.0	50.0
Min : Max	11 : 68	19 : 69	11 : 69
Duration of GLP-1 receptor agonist treatment (years)			
Number	257	257	514
Mean (SD)	1.89 (1.76)	1.92 (1.85)	1.90 (1.81)
Median	1.17	1.13	1.17
Min : Max	0.3 : 13.0	0.3 : 12.1	0.3 : 13.0
GLP-1 receptor agonist use by type at screening in eCRF [n (%)]			
Number	257	257	514
Once/twice daily formulation	153 (59.5%)	154 (59.9%)	307 (59.7%)
Once weekly formulation	104 (40.5%)	103 (40.1%)	207 (40.3%)
Daily dose of liraglutide (mg) at baseline			
Number	135	145	280
Mean (SD)	1.66 (0.25)	1.66 (0.28)	1.66 (0.27)
Median	1.80	1.80	1.80
Min : Max	1.2 : 1.8	1.2 : 3.0	1.2 : 3.0
Daily dose of exenatide (µg) at baseline			
Number	18	9	27
Mean (SD)	18.33 (3.83)	17.78 (4.41)	18.15 (3.96)
Median	20.00	20.00	20.00
Min : Max	10.0 : 20.0	10.0 : 20.0	10.0 : 20.0

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
Diabetic retinopathy [n (%)]			
Number	257	257	514
Yes	20 (7.8%)	14 (5.4%)	34 (6.6%)
No	237 (92.2%)	243 (94.6%)	480 (93.4%)
Diabetic proliferative retinopathy [n (%)]			
Number	257	257	514
Yes	2 (0.8%)	2 (0.8%)	4 (0.8%)
No	255 (99.2%)	255 (99.2%)	510 (99.2%)
Diabetic neuropathy [n (%)]			
Number	257	257	514
Yes	62 (24.1%)	59 (23.0%)	121 (23.5%)
No	195 (75.9%)	198 (77.0%)	393 (76.5%)
Diabetic nephropathy [n (%)]			
Number	257	257	514
Yes	20 (7.8%)	26 (10.1%)	46 (8.9%)
No	237 (92.2%)	231 (89.9%)	468 (91.1%)
Baseline urinary albumin/creatinine ratio (mg/g) [n (%)]			
Number	253	256	509
< 30 (normal)	197 (77.9%)	203 (79.3%)	400 (78.6%)
≥ 30 to < 300 (microalbuminuria)	48 (19.0%)	45 (17.6%)	93 (18.3%)
≥ 300 (macroalbuminuria)	8 (3.2%)	8 (3.1%)	16 (3.1%)
Estimated eGFR at screening ($mL/min/1.73m^2$)			
Number	257	257	514
Mean (SD)	88.96 (24.87)	85.71 (22.60)	87.34 (23.79)
Median	86.25	84.06	85.20
Min : Max	40.9 : 296.4	39.5 : 171.8	39.5 : 296.4
Estimated eGFR at screening ($mL/min/1.73m^2$) [n (%)]			
Number	257	257	514
< 15 (End stage renal disease)	0	0	0
≥ 15 - < 30 (Severe decrease in GFR)	0	0	0
≥ 30 - < 60 (Moderate decrease in GFR)	17 (6.6%)	31 (12.1%)	48 (9.3%)
≥ 60 - < 90 (Mild decrease in GFR)	132 (51.4%)	126 (49.0%)	258 (50.2%)
≥ 90 (Normal)	108 (42.0%)	100 (38.9%)	208 (40.5%)
Use of both Pioglitazone, and SGLT2 inhibitor at screening [n (%)]			
Number	257	257	514
Yes	1 (0.4%)	1 (0.4%)	2 (0.4%)
No	256 (99.6%)	256 (99.6%)	512 (99.6%)

SGLT2 = Sodium glucose co-transporter 2, eGFR = estimated Glomerular Filtration Rate.
Duration of diabetes (years) = (Date of informed consent - Date of diagnosis of diabetes + 1)/365.25
Age at onset of Type 2 diabetes (years) = (year of diagnosis of diabetes - year of birth)
eGFR is derived using the 4 variable Modification of Diet in Renal Disease formula.
Urine albumin/creatinine ratio is presented in mg/g, and the conversion factor to the standard international unit mg/mmol is 0.1130.
*: one patient(ID: 124000100004) with dose of 3.0mg was included.

Table 6 - Efficacy variables at baseline

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
HbA1c (%)			
Number	257	257	514
Mean (SD)	7.78 (0.62)	7.80 (0.56)	7.79 (0.59)
Median	7.70	7.80	7.70
Min : Max	6.5 : 10.0	6.2 : 9.3	6.2 : 10.0
FPG (mmol/L)			
Number	257	257	514
Mean (SD)	9.09 (2.15)	9.42 (1.94)	9.26 (2.05)
Median	8.70	9.10	8.88
Min : Max	5.1 : 18.6	4.4 : 16.3	4.4 : 18.6
Average 7-point SMPG (mmol/L)			
Number	246	243	489
Mean (SD)	9.44 (1.91)	9.56 (1.77)	9.50 (1.84)
Median	9.12	9.25	9.19
Min : Max	5.9 : 15.6	6.1 : 15.4	5.9 : 15.6
2-hour postprandial plasma glucose (mmol/L)			
Number	241	240	481
Mean (SD)	13.70 (3.42)	13.76 (3.26)	13.73 (3.34)
Median	13.32	13.63	13.43
Min : Max	5.1 : 23.1	5.9 : 26.1	5.1 : 26.1
2-hour glucose excursion (mmol/L)			
Number	241	240	481
Mean (SD)	4.36 (2.72)	4.20 (2.63)	4.28 (2.67)
Median	4.20	4.14	4.20
Min : Max	-6.3 : 13.9	-4.3 : 13.8	-6.3 : 13.9
Weight (kg)			
Number	257	257	514
Mean (SD)	92.87 (16.36)	95.49 (16.90)	94.18 (16.67)
Median	92.00	94.50	93.85
Min : Max	53.0 : 135.8	50.0 : 139.8	50.0 : 139.8

FPG = Fasting Plasma Glucose, SMPG = Self-monitored plasma glucose.

Numbers analysed

The efficacy analyses based on the mITT population included 505 patients (252 [98.1%] patients in the FRC group and 253 [98.4%] patients in the GLP-1 RA group). In addition, 2 patients in the FRC group were excluded from the primary efficacy analyses because they did not have post-baseline HbA1c data (***Table 7***).

Table 7 – Analysis populations

	Fixed Ratio Combination	GLP-1 Receptor Agonist	All
Randomized population	257 (100%)	257 (100%)	514 (100%)
Efficacy population			
Modified Intent-to-Treat (mITT)	252 (98.1%)	253 (98.4%)	505 (98.2%)
Safety population	255	256	511
PK population	244		

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

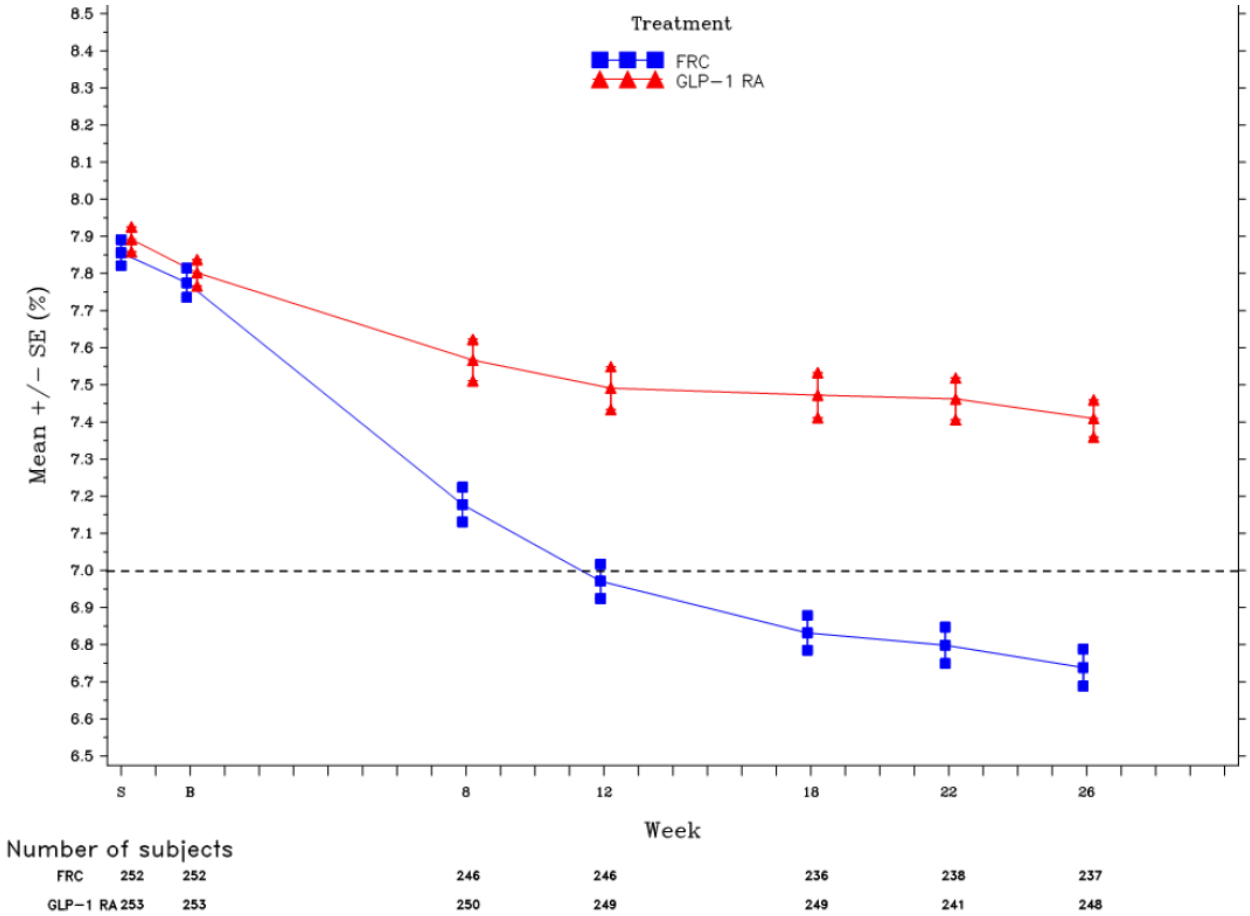
Outcomes and estimation

Change in HbA1c (%) from baseline to Week 26 (primary endpoint)

Mean HbA1c levels throughout the duration of the trial are depicted by treatment group in ***Figure 3***. Mean HbA1c at baseline was 7.7% in the FRC group and 7.8% in the GLP-1 RA group. After 26 weeks of treatment, HbA1c had on average decreased by -1.02% for the FRC group and -0.38% for the GLP-1 RA group, a mean value at Week 26 of 6.74% and 7.41%, respectively. In both treatment groups, mean HbA1c decreased during the study with the lowest mean HbA1c value at Week 26.

The reduction in HbA1c from baseline to Week 26 was statistically significant greater in the group treated with FRC vs GLP-1 RA (LS mean difference: -0.64%; 95% CI: -0.770 to -0.508; p <0.0001). Four sensitivity analyses showed consistent results with the primary analysis.

Figure 3 - Mean change in HbA1c (%) from baseline to Week 26 using MMRM – mITT population



S = Screening (Week -2), B = Baseline
FRC = Fixed Ratio Combination, GLP-1RA = GLP-1 Receptor Agonist
The plot included all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue medication.

Secondary endpoints

Responders for HbA1c after 26 weeks of treatment

At Week 26, the percentage of patients reaching HbA1c <7% was significantly higher in the FRC group (61.9%) compared with the GLP-1 RA group (25.7%) (p<0.0001) (***Table 8***). The percentage of patients reaching HbA1c ≤6.5% was also markedly higher in the FRC group (p<0.0001).

Table 8 - Number (%) of patients with HbA1c value <=6.5% or <7% at Week 26 - mITT population

HbA1c (%)	Fixed Ratio Combination (N=252)	GLP-1 Receptor Agonist (N=253)
Number	252	253
≤6.5 %	102 (40.5%)	25 (9.9%)
Proportion difference (95% CI) vs. GLP-1 RA[a]	30.61% (23.61% to 37.62%)	-
p-value	<.0001	-
<7 %	156 (61.9%)	65 (25.7%)
Proportion difference (95% CI) vs. GLP-1 RA[a]	36.05% (28.11% to 43.99%)	-
p-value	<.0001	-

GLP-1 RA = GLP-1 receptor agonist

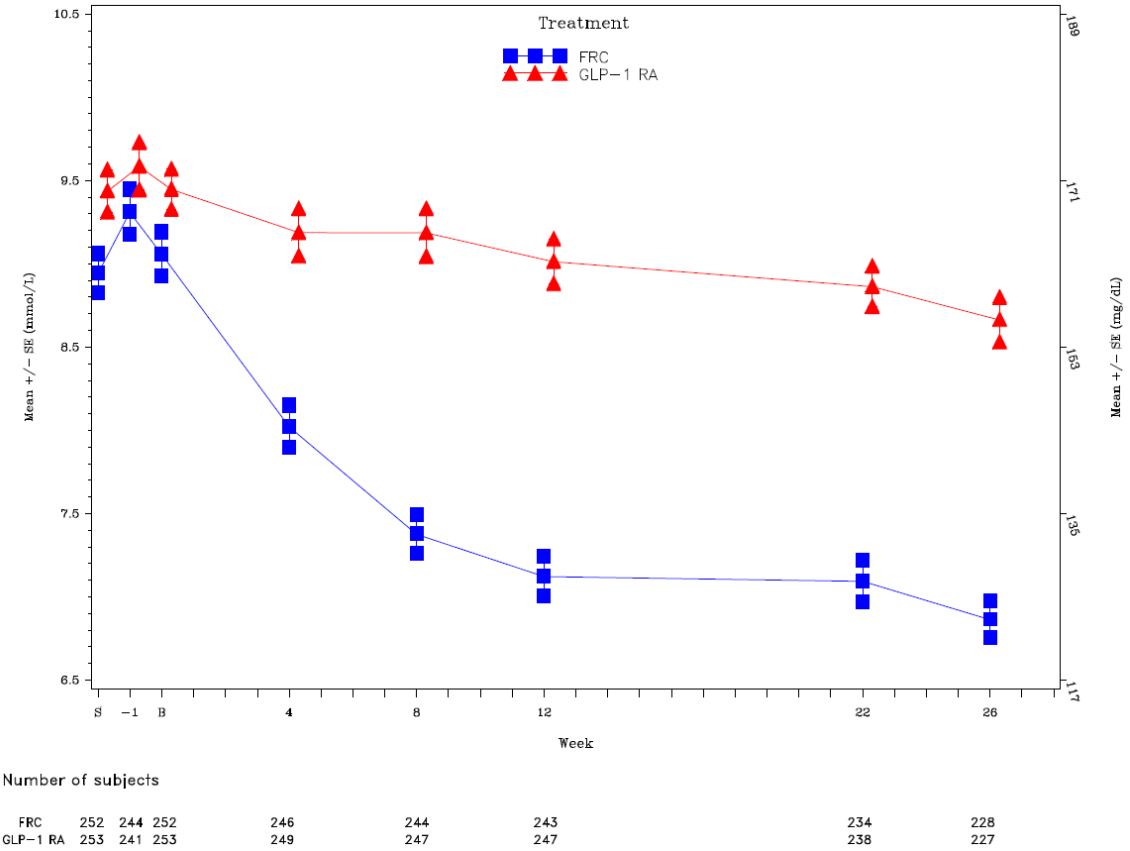
a Weighted average of proportion difference between treatment groups (fixed ratio combination vs. GLP-1 receptor agonist) from each stratum (randomization strata of HbA1c [<8.0 or ≥8.0 %] at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype [once/twice daily formulations, once weekly formulations] at screening) using Cochran-Mantel-Haenszel weights.

Proportion difference = difference of the proportions of patients achieving HbA1c value ≤6.5% or <7%.
All measurements at week 26 were used, including those obtained after IMP discontinuation or introduction of rescue therapy. If no assessment was available at week 26 at all, patients were treated as non-responders.

Fasting plasma glucose

The reduction from baseline to Week 26 in fasting plasma glucose was significantly greater in the FRC group (-2.28 mmol/L [-40.99 mg/dL]) compared to the GLP-1 RA group (-0.6 mmol/L [-10.88 mg/dL]). The LS mean difference between the treatment groups was -1.67 mmol/L (-30.10 mg/dL) (p<0.0001). in In the FRC group, FPG reduction mainly occurred during the initial 8 to 12 weeks of treatment, and FPG trended toward stabilization after Week 12 (***Figure 4***).

Figure 4 - Plot of mean fasting plasma glucose (mmol/L[mg/dL] by visit during the 26-week randomized treatment period - mITT population



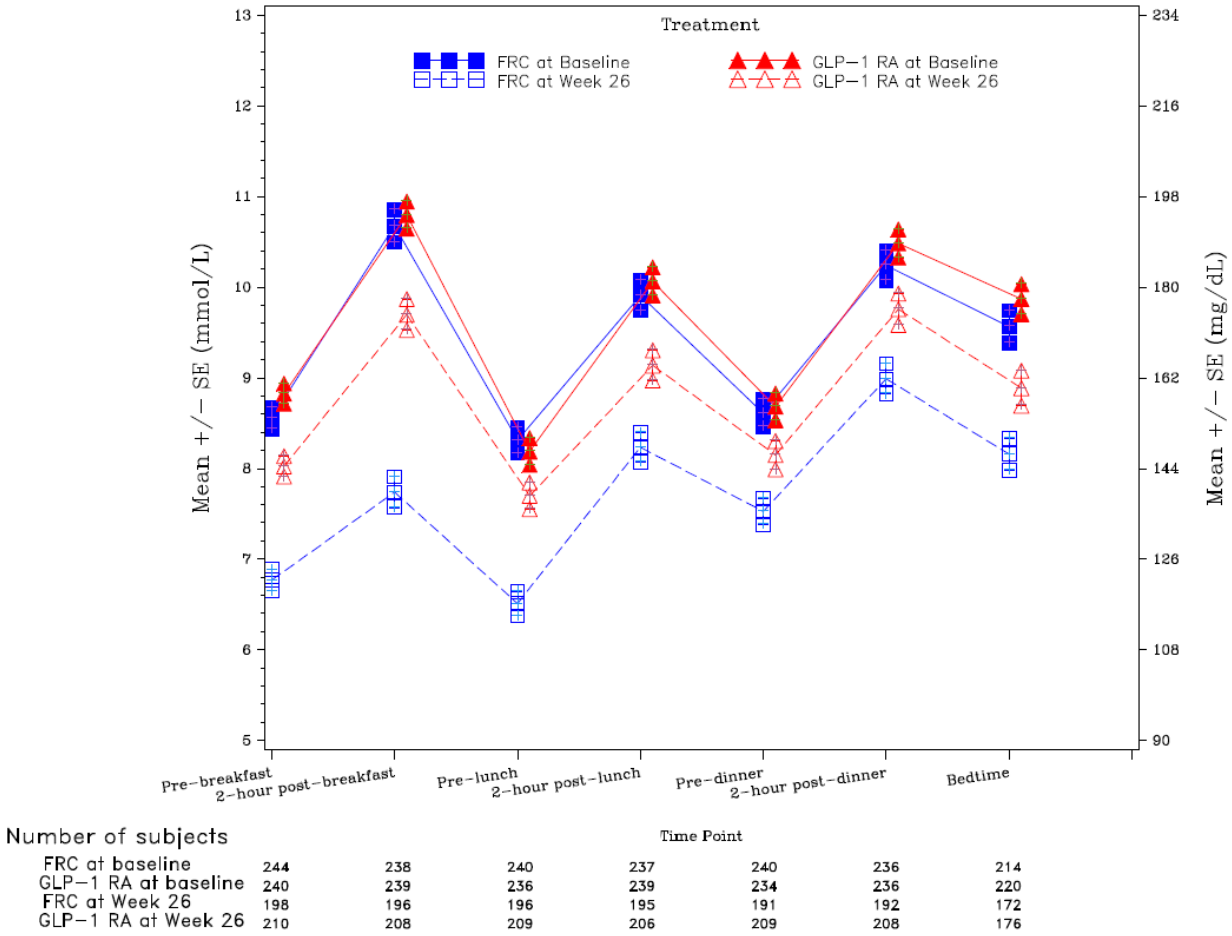
7-point self-monitored plasma glucose profile

The reduction from baseline to Week 26 in the average daily 7-point SMPG was significantly greater in the FRC group (-1.69 mmol/L [-30.36 mg/dL]) compared to the GLP-1 RA group (-0.67 mmol/L [-12.06 mg/dL]). The LS mean difference between the treatment groups was -1.02 mmol/L (-18.31 mg/dL) (p<0.0001) The 7-point SMPG profiles in the FRC group showed a marked decrease from baseline in mean plasma glucose values at Week 26 at all time points. The mean plasma glucose values at all time points were lower in the FRC group compared to the GLP-1 RA group (***Figure 5***).

Prandial glycaemic control during a standardized meal test

Treatment with the FRC improved postprandial glycaemic control after a standardized liquid breakfast in comparison to GLP-1 RA (-3.96 mmol/L [-71.32 mg/dL] in the FRC group and -1.11 mmol/L [-19.99 mg/dL] in the GLP-1 RA group. The LS mean difference between the treatment groups was -2.85 mmol/L (-51.33 mg/dL) (p<0.0001) There was also a greater reduction from baseline in 2-hour plasma glucose excursion for the FRC compared to GLP-1 RA: -1.51 mmol/L (-27.20 mg/dL) in the FRC group and -0.52 mmol/L (-9.40 mg/dL) in the GLP-1 RA group. The LS mean difference between the 2 treatment groups was −0.99 mmol/L (p<0.0001)

Figure 5 - Plot of mean 7-point SMPG (mmol/L [mg/dL]) at baseline and Week 26 - mITT population



SMPG = Self-monitored plasma glucose.
FRC = Fixed Ratio Combination, GLP-1 RA=GLP-1 Receptor Agonist
The analysis included all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy.

Body weight

Body weight increased in the FRC group and decreased in the GLP-1 RA group with a LS mean change from baseline to Week 26 of +1.89 kg and -1.14 kg, respectively (LS mean difference was 3.03 kg; 95% CI: 2.417 kg to 3.643 kg).

Percentage of patients requiring rescue therapy

The percentage of patients who required rescue therapy was lower in the FRC group (4.8%) compared to the GLP-1 RA group (15.0%), with a risk difference of -10.00% (95% CI: -14.93%, -5.06%). Of the 12 patients requiring rescue therapy in the FRC group, 11 had reached the 60 U dose.

Insulin glargine and lixisenatide dose in the FRC group

For the FRC group, the mean daily FRC dose increased steadily during the study and reached at Week 26 a mean dose of 43.5 U for the insulin glargine component and 16.55 µg for the lixisenatide component. The final FRC dose at the end of the 26-week randomized treatment period was ≥30 U and ≤60 U for 79.6% of the patients, with 67 patients (26.3%) receiving the maximum daily dose of 60 U. For the subgroup reaching the maximum dose (60 U), the mean HbA1c level at Week 26 was 6.87%, compared to 6.69% for those having a final dose <60 U. In the subgroup reaching the maximum FRC dose, 50.7%

of the patients had an HbA1c level <7% at Week 26 versus 65.9% for the subgroup having a final dose <60 U.

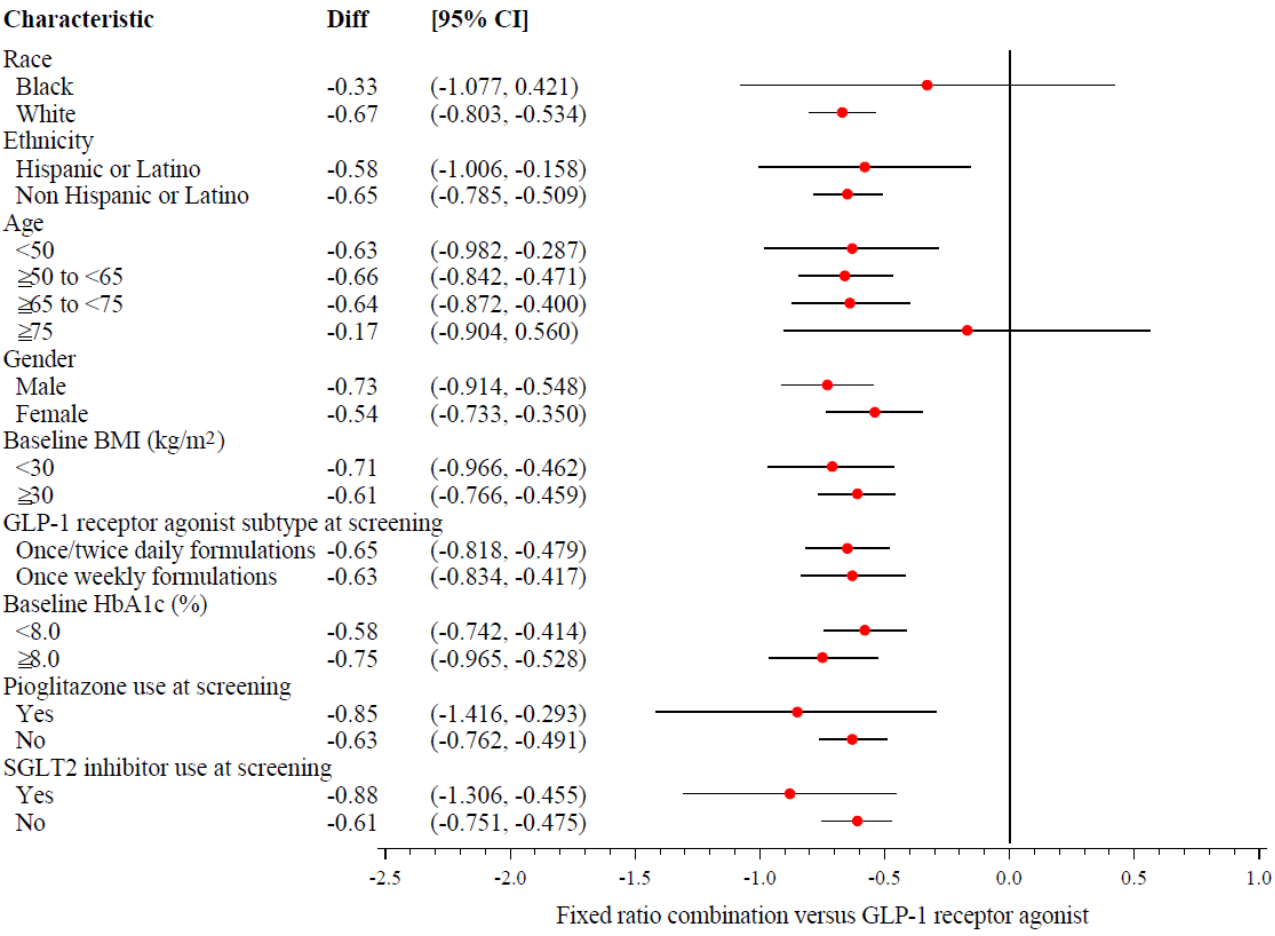
Patients reaching HbA1c <7% (53 mmol/mol) with no body weight gain from baseline to Week 26

At Week 26, the percentage of patients reaching HbA1c <7% (53 mmol/mol) with no body weight gain was 23.0% in the FRC group and 20.9% in the GLP-1 RA group during the 26-week randomized treatment period.

Ancillary analyses

Subgroup analysis of the primary efficacy analysis by baseline factors showed consistent treatment effects across most subgroups, including the type of previous GLP-1 RA treatment and the use of SGLT-2 inhibitors at screening. The 95% CI of the between-group difference included 0 in the subgroups of black patients (N=17) and patients aged ≥75 years at screening (N=21) (***Figure 6***). However, due to limited number of patients in these subgroups and the wide CIs, these results should be interpreted with caution.

Figure 6 - Forest plot of mean change in HbA1c (%) by baseline factor – mITT population



The post-hoc analysis of the proportion of patients reaching the HbA1c <7% target at Week 26 without documented symptomatic hypoglycaemia showed that markedly more patients in the FRC group reached this composite endpoint versus the GLP-1 RA group for the plasma glucose threshold ≤3.9 mmol/L (≤70 mg/dL) (43.3% and 25.3% respectively) and for the threshold <3.0 mmol/L [<54 mg/dL]) (56.7% and 25.3% respectively).

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9. Summary of Efficacy for trial EFC13794

Title: A 26-week randomized, open-label, active controlled, parallel-group, study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with Type 2 Diabetes inadequately controlled on GLP-1 receptor agonist and metformin (alone or with pioglitazone and/or SGLT-2 inhibitors), followed by a fixed ratio combination single-arm 26-week extension period			
Study identifier	EFC13794		
Design	26-week randomized, open-label, active controlled, parallel-group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 weeks Up to 2 weeks 26 weeks (not included in this application)	
Hypothesis	Superiority of FRC vs unchanged therapy		
Treatments groups	FRC	Suliqua (insulin glargine/lixisenatide). 26-week, 257	
	GLP-1 RA	GLP-1RA + metformin ± pioglitazone ± SGLT2i. 26-week, 257	
Endpoints and definitions	**Primary endpoint**	HbA1c	Change in HbA1c from baseline to Week 26
	Secondary endpoint	FPG	Change in FPG from baseline to Week 26
	Secondary endpoint	2-hour PPG	Change in 2-hour PPG and in blood glucose excursion during standardized meal test from baseline to Week 26
	Secondary endpoint	Weight	Change in body weight from baseline to Week 26
	Secondary endpoint	HbA1c <7%	Percentage of patients reaching HbA1c <7% (53 mmol/mol) at Week 26
	Secondary endpoint	Rescue therapy	Percentage of patients requiring rescue therapy during the 26-week treatment period
Database lock	09 July 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified intent-to-treat population - 26 weeks from baseline		
Descriptive statistics and estimate variability	Treatment group	FRC (insulin glargine/lixisenatide)	GLP-1 RA
	Number of subjects	252	253
	HbA1c (%)	-1.02 ±	-0.38
	SE	0.048	0.048
	FPG (mmol/mol)	-2.28	-0.60
	SE	0.120	0.119
	2-hour PPG (mmol/mol)	-3.96	-1.11
	SE	0.211	0.205
	Body weight (kg)	1.89	-1.14
	SE	0.222	0.220

	HbA1c <7% (n (%))		156 (61.9%)	65 (25.7%)
	Rescue therapy (n (%))		12 (4.8)	38 (15.0%)
Effect estimates per comparison	HbA1c	Comparison groups	FRC vs GLP-1 RA	
		LS Mean difference (SE)	-0.64 (0.067)	
		95% CI	(-0.770 to -0.508)	
		P-value	<0.0001	
	FPG	Comparison groups	FRC vs GLP-1 RA	
		LS mean difference (SE)	-1.67 (0.168)	
		95% CI	-2.001 to -1.341	
		P-value	<0.0001	
	2-hour PPG	Comparison groups	FRC vs GLP-1 RA	
		LS mean difference (SE)	-2.85 (0.290)	
		95% CI	-3.420 to -2.279	
		P-value	<0.0001	
	Body weight	Comparison groups	FRC vs GLP-1 RA	
		LS Mean difference (SE)	3.03 (0.312)	
		95% CI	2.417 to 3.643	
		P-value	n/a	
	HbA1c <7%	Comparison groups	FRC vs GLP-1 RA	
		Proportion difference (%)	36.05%	
		95% CI	28.11% to 43.99%	
		P-value	<.0001	
	Rescue therapy	Comparison groups	FRC vs GLP-1 RA	
		Risk difference (%)	-10.00%	
		95% CI	-14.93% to -5.06%	
		P-value	n/a	

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

This dossier is based on a single Phase 3b Study (EFC13794) and therefore, no pooling of studies was performed.

In Study EFC13794, the overall treatment effect of FRC on glycaemic control in patients with T2DM who were inadequately controlled with OAD therapy and GLP-1 RA therapy was consistent with that observed in the previously submitted Phase 3 pivotal studies EFC12404 and EFC12405 in patients with T2DM who were inadequately controlled with OAD therapy ± basal insulin (***Table 10***).

Table 10 - Comparison of key efficacy results with FRC in pivotal Phase 3 studies

Endpoints	Studies		
	EFC13794[a]	EFC12404[b]	EFC12405[c]
	N= 252	N=468	N=366
HbA1c			
Baseline mean (SD) (%)	7.77 (0.63)	8.08 (0.71)	8.07 (0.68)
LS Mean (SE) change from baseline to post-baseline[d] (%)	-1.02 (0.048)	-1.63 (0.038)	-1.13 (0.057)
Responders, HbA1c <7.0%	61.9%	73.7%	54.9%
Responders, HbA1c ≤6.5%	40.5%	55.8%	33.9%
2-hour PPG (mmol/L)			
LS mean (SE) change from baseline to post-baseline[d]	-3.96 (0.211)	-5.68 (0.176)	-4.72 (0.322)
2-hour PPG excursions (mmol/L)			
LS mean (SE) change from baseline to post-baseline[d]	-1.51 (0.177)	-2.31 (0.154)	-3.90 (0.285)
FPG (mmol/L)			
LS mean (SE) change from baseline to post-baseline[d]	-2.28 (0.120)	-3.46 (0.090)	-0.35 (0.142)

PPG, postprandial glucose; FPG, fasting plasma glucose; LS, least square

a Population: patients with T2DM inadequately controlled with oral antidiabetic drug (OAD) and GLP-1 receptor agonist (RA) therapy

b Population: patients with T2DM inadequately controlled with oral antidiabetic drug (OAD) therapy

c Population: patients with T2DM inadequately controlled with oral antidiabetic drug (OAD) + basal insulin therapy

d Post-baseline is Week 26 in Study EFC13794 and Week 30 in Studies EFC12404 and EFC12405

Source: Table 2, Table 3, Table 4, Table 6, Table 7. CSR EFC12404 Tables 15, 18, 19, 20, 22; CSR EFC12405 Tables 16, 19, 20, 21, 30

Clinical studies in special populations

No dedicated studies in special populations were performed. The number of patients ≥75 years was small (6/252 in the FRC group and 15/253 in the GLP-1 RA group), therefore no conclusions on treatment efficacy can be made in this patient group.

No patients with eGFR < 30 (mL/min/1.73m2) were included in study EFC13794.

Supportive studies

In order to support the extension of the indication to allow concomitant treatment with metformin with or without SGLT-2 inhibitors, data from two additional clinical trials were provided.

Study EFC14112, a randomized, 26-week, active-controlled, open-label, 2-treatment arm, parallel-group and multicentre study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed-ratio combination to lixisenatide on top of oral antidiabetic drugs in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs with a 26-week safety extension period.

In this study, 34 patients (21.1%) received concomitantly the FRC and a SGLT2i.

In both treatment groups, patients receiving a SGLT2i at screening tended to be younger, had slightly higher BMI and shorter diabetes duration as compared to those not receiving a SGLT2i inhibitor. Otherwise baseline demographics, patient and disease characteristics were similar.

The difference between the FRC and lixisenatide treatment groups in LS mean HbA1c change from baseline was -1.00% (95% CI: -1.429, -0.573) in the subgroup of SGLT2i users, and -1.11% (95% CI: -1.325 to -0.890) in SGLT2i non-users. Although small and not relevant differences can be observed, efficacy results (change from baseline to Week 26 in HbA1c and FPG) in both FRC and lixisenatide treatment groups were generally similar in SGLT2i users and non-users. The results are consistent with those observed for the entire population.

Study EFC14114, a randomized, 26-week, active-controlled, open-label, 2-treatment arm, parallel-group and multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed-ratio combination to insulin glargine on top of oral antidiabetic drugs in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs.

In this study, 59 patients (22.7%) received concomitantly the FRC and a SGLT2i.

In both treatment groups, patients receiving a SGLT2i at screening tended to be younger, had slightly higher BMI and shorter diabetes duration as compared to those not receiving a SGLT2i. Otherwise, baseline demographics, patient and disease characteristics were similar.

The difference between the FRC and insulin glargine treatment groups in LS mean HbA1c change from baseline was -0.70% (95% CI: -0.952, -0.455) in the subgroup of SGLT2i users, and -0.65 (95% CI: -0.780 to -0.518) in SGLT2i non-users. Although small and not relevant differences can be observed, efficacy results (change from baseline to Week 26 in HbA1c, FPG and 2-hour PPG) in both FRC and insulin glargine treatment groups were generally similar in SGLT2i users and non-users. In particular there was no indication of a decreased efficacy of the FRC in the SGLT2i user subgroup and the results were consistent with those observed for the entire population.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study EFC13794 was designed to assess the efficacy and safety of the FRC of insulin glargine and lixisenatide in patients with T2DM who were inadequately controlled with GLP-1 RAs in combination with OADs. Previous Phase 3 clinical trials have supported the use of the FRC in patients with insufficient glycaemic control with OADs (insulin naïve) or basal insulin in combination with OADs (without GLP1-RA treatment). The FRC has only been indicated in combination with metformin.

The study had a 1:1 randomized, active-controlled, 2-arm, 26-week treatment duration, parallel group, multinational and multicenter Phase 3b design. At the end of the study, patients in the FRC group were offered the possibility to enter an FRC single-arm 26-week extension period (data not included in this application). Patients were stratified according to HbA1c (<8%, ≥8%) and GLP-1 RA subtype (once/BID formulations, QW formulations). Trial design is considered adequate. The objectives as well as the primary and secondary endpoints were relevant.

This study included 514 patients with T2DM inadequately controlled with daily (about 60% of the patients) or weekly (approximately 40%) GLP-1 RAs combined with metformin with or without pioglitazone and/or an SGLT-2 inhibitor. At screening, 16.3% of patients were treated with metformin and another OAD (SGLT-2 inhibitors [10.1%] and/or pioglitazone [6.6%]). The most common GLP-1 RAs received at screening were liraglutide (54.5%) and dulaglutide (20.4%).

The reasons for choosing an open-label design are understood and accepted although it should be kept in mind that the fact that this could introduce bias regarding both the efficacy and safety assessments. Patients randomised to their usual treatment may be less prone to intensify their background treatment

whereas patients on the new treatment may be more motivated for lifestyle changes. The awareness for adverse events could also be affected by the open-label design.

The inclusion and exclusion criteria were adequate and reflect the proposed target population. Patients with a BMI>40, severe renal impairment or hepatic impairment were not included. It is worth noting that patients with significant concomitant illnesses (e.g. cardiovascular) were excluded.

Patients entering the study were randomized to either FRC or unchanged GLP-1 RA, both on top of OAD therapy (metformin ± pioglitazone ± SGLT-2 inhibitors). In the comparator/reference group arm, a wide range of currently available GLP-1 RAs were selected. The choice of comparator is adequate, considering the primary objective of the study, which is to investigate the transfer from any GLP-1 RA to Suliqua.

For the FRC, a titration algorithm was provided. The dosing recommendations were based on the approved product information. As in previous phase 3 trials, two pens with different insulin glargine/lixisenatide fixed ratios were used.

The sample size calculation has considered the fact that missing data will be imputed with a "jump to reference" method and hence dilute the treatment effect. This is encouraged. The true mean difference between FRC and GLP-1 receptor agonist in change in HbA1c from baseline to Week 26 is assumed to be 0.4%.

The mITT population used for efficacy analyses required patients to have post-baseline assessment of efficacy for inclusion. This is not strictly according to the ITT principle and might in theory introduce a bias in the comparison between treatment groups. However, less than 2% of patients were excluded from the mITT population and hence this is accepted.

Four sensitivity analyses were performed on the primary efficacy endpoint, whereof one was based on a missing not at random assumption. The sensitivity analyses described address slightly different estimands as compared to the primary analysis. With the small amount of missing data presented in this study, the sensitivity analyses are considered adequate.

The type I error is controlled with a hierarchical testing procedure which is accepted. The statistical methods were adequate.

The study appears adequately conducted. One major protocol deviation related to the randomization procedure was adequately handled. Two major amendments where done to the original protocol dated 11 February 2016, being the most important the inclusion of patients treated with SGLT2i.

The baseline demographics seems to be well-balanced between study groups. The study population was representative of inadequately controlled T2D patients, thus qualifying for intensification of therapy. The study groups had a similar HbA1c at baseline. Stratification by HbA1c and type of GLP1-RA was similar between groups. The majority of patients were obese (72.8 %).

Disease characteristic and metabolic control were similar between study groups. Patients with severe renal impairment were not included in the study. This is accepted as the use of Suliqua has not been investigated this patient group.

Efficacy data and additional analyses

The study EFC13794 met the primary objective, showing a difference of 0.64% in HbA1c in favour of the FRC group after 26 weeks. The difference was already seen at 8 weeks. Significantly more patients reached the 7.0 % HbA1c target in the FCR treated group (respectively 61.9% and 25.7%) ($p<0.0001$).

Starting from slightly different baseline levels (9.06 mmol/L for FRC and 9.45 mmol/L for GLP-1 RA), the reduction in FPG was greater in the FRC group compared to the GLP-1 RA group ($p<0.0001$), and patients

in the FRC group reported a greater decrease in the average 7-point SMPG profile from baseline to Week 26 compared to patients in the GLP-1 RA group ($p<0.0001$). Seven-point SMPG profiles showed that values at all Week 26 time points were reduced from baseline and lower in the FRC group compared to the GLP-1 RA group.

Treatment with FRC improved prandial glycaemic control during a standardized meal test compared to GLP-1 RA, as shown by the results of change from baseline in 2-hour PPG (treatment difference: -2.85 mmol/L [-51.33 mg/dL], $p<0.0001$) as well as in 2-hour plasma glucose excursions (treatment difference: -0.99 mmol/L [-17.80 mg/dL], $p<0.0001$).

As expected, body weight increased in the FRC group and decreased in the GLP-1 RA, due to the addition of insulin treatment (+1.89 kg and -1.14 kg, respectively; LS mean difference was 3.03 kg).

The percentage of patients requiring rescue therapy in the FRC group (4.8%) was lower compared to the GLP-1 RA group (15.0%).

The mean daily insulin dose increased over the study period, reaching a mean value of 43.50 U (0.46 U/kg) at Week 26. Most patients (79.6%) had final insulin daily doses of ≥30 U to ≤60 U. At week 26, the mean daily dose of the lixisenatide component in the FRC group was 16.55 µg/day, and most patients (75.3%) had a final dose of ≥15 to ≤20 µg.

Ancillary analyses support the primary outcome. No conclusion can be made on the effect of the FRC in black patients and those >75 years old due to the limited amount or data.

The effects related to glycaemic control of the FRC observed in this population were consistent with those observed in the overall population of Phase 3 studies. Following the switch from the pre-trial GLP-1 RA, no relevant increase in mean fasting SMPG values was observed during the first 4 weeks of treatment, mitigating the risk of potential deterioration of glycaemic control after switch from pre-trial GLP-1 RA to FRC.

Data from the subgroup analysis in patients treated with SGLT-2 inhibitors in study EFC13794 together with supportive data from two Japanese studies were provided to support the concomitant use of the FRC with SGLT-2 inhibitors. The efficacy data for this group were consistent across the different studies showing an added benefit of SGLT-2 inhibitors.

2.4.3. Conclusions on the clinical efficacy

Study EFC13794 was designed to assess the efficacy and safety of the FRC Suliqua (insulin glargine and lixisenatide) in patients with T2DM who were inadequately controlled with GLP-1 RAs in combination with OADs. Suliqua is already approved in patients treated with metformin alone or combined with OADs (insulin naïve) or those on basal insulin in combination with OADs.

The data shown in Study EFC13794 provide evidence that T2DM patients with suboptimal metabolic control on GLP1-RA may benefit from the addition of basal insulin by switching incretin therapy to the FRC of Suliqua. The study also provides limited information on the concomitant use of Suliqua and pioglitazone and/or SGLT2i in addition to metformin. The use of Suliqua concomitantly with SGLT-2 inhibitors was further supported by subgroups from 3 prospective clinical studies. Even if the data are limited, SGLT2i seem to have an added benefit when combined with the FRC.

No further measures are considered necessary to address issues related to clinical efficacy.

2.5. Clinical safety

Introduction

The safety evaluation of this variation is based on data collected during the first 26-week (randomized) of Study EFC13794. The cut-off date for this dossier was 09 July 2018 (database lock of the first 26-week [randomized] treatment period). No pooling of studies was performed for safety. The 26-week extension period is ongoing.

Patient exposure

The safety population of Study EFC13794 consisted of all randomized patients who received at least 1 dose of open-label drug (regardless of the amount of treatment administered). Patients were analysed for safety analyses according to the actual treatment received.

Of the 840 patients screened, 514 were randomized (257 patients in each treatment group). The percentage of patients completing the 26-week randomized treatment period was high in both treatment groups (89.5% in the FRC group and 95.7% in the GLP-1 RA group). The most common reason for discontinuation were other reasons (not caused by adverse events, hypoglycaemia, lack of efficacy or poor compliance to protocol) and AEs in the FRC group (4.7% and 3.9%, respectively).

During the 26-week randomized treatment period, the cumulative duration of treatment exposure was similar between the two treatment groups, 121 PY and 127 PY for FRC and GLP-1 RA group, respectively (***Table*** 11). Median treatment duration was 183 days in both treatment groups. The majority of patients in both treatment groups were exposed for ≥169 days (90.2% in the FRC group and 95.7% in the GLP-1 RA group).

Table 11 - Exposure to investigational medicinal product during the 26-week randomized treatment period – Safety population

	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Cumulative duration of treatment exposure (patient years)	121.4	127.0
Duration of study treatment (days)		
Number	255	256
Mean (SD)	173.9 (35.7)	181.2 (22.7)
Median	183.0	183.0
Min : Max	1 : 209	15 : 222
Duration of study treatment by category [n (%)]		
Missing duration	0	0
1-14 days	4 (1.6%)	0
15-28 days	3 (1.2%)	2 (0.8%)
29-56 days	2 (0.8%)	1 (0.4%)
57-84 days	2 (0.8%)	3 (1.2%)
85-126 days	10 (3.9%)	1 (0.4%)
127-168 days	4 (1.6%)	4 (1.6%)
169-182 days	45 (17.6%)	76 (29.7%)
>182 days	185 (72.5%)	169 (66.0%)
Cumulative duration of study treatment by category [n (%)]		
Missing duration	0	0
≥ 1 day	255 (100%)	256 (100%)
≥ 15 days	251 (98.4%)	256 (100%)
≥ 29 days	248 (97.3%)	254 (99.2%)
≥ 57 days	246 (96.5%)	253 (98.8%)
≥ 85 days	244 (95.7%)	250 (97.7%)
≥ 127 days	234 (91.8%)	249 (97.3%)
≥ 169 days	230 (90.2%)	245 (95.7%)
≥ 182 days	185 (72.5%)	169 (66.0%)

IMP: Investigational Medicinal Product
For daily formulation, duration of exposure = (date of the last open-label IMP injection - date of the first open-label IMP injection) + 1.
For weekly formulation, duration of exposure = (date of the last open-label IMP injection - date of the first open-label IMP injection) + 7.
Note: Patients are considered in the treatment group they actually received at randomization.

Adverse events

Definition of safety variables in Study EFC13794 was consistent with the safety analyses performed in previous Phase 2/3 studies. Safety analysis focused on the following variables:

- Symptomatic hypoglycaemia (documented, probable, severe symptomatic hypoglycaemia);
- Adverse events (AEs) and serious adverse events (SAEs);

- Adverse events of special interest (AESI): confirmed alanine aminotransferase (ALT) increase >3 x upper limit of the normal (ULN), pregnancy occurring in a female patient entered in the study or in a female partner of a male patient entered in a study with IMP/non-investigational medicinal product (NIMP), and symptomatic overdose with IMP or NIMP;
- Other significant AEs: AEs related to injection site reactions, allergic/hypersensitivity events, pancreatic events, patients with increased calcitonin ≥20 pg/mL, and device-related events (DREs);
- Safety laboratory values, vital signs, and electrocardiograms (ECGs)
- Immunogenicity (FRC group): anti-insulin antibodies (AIAs) and anti-lixisenatide antibodies (ADAs).

Adjudication committees

Two external and independent adjudication committees (listed below) reviewed and adjudicated events reported during the study using blinded data:

- The Allergic Reaction Assessment Committee (ARAC) adjudicated allergic or possible allergic events;
- The Pancreatic Safety Assessment Committee (PSAC) adjudicated pancreatic events.

Common adverse events

Treatment-emergent adverse events (TEAEs) observed in Study EFC13794 during the 26-week treatment period are summarized in ***Table 12*** . The percentage of patients who had at least one TEAE was higher in the FRC group than in the GLP-1 RA group (163 patients [63.9%] vs. and 121 patients [47.3%]). The rate of serious TEAEs was similar in both treatment groups (3.9% in the FRC group and 3.5% in the GLP-1 RA group) (***Table 12***). The percentage of patients who permanently discontinued due to a TEAE was higher in the FRC group (3.5%) compared with the GLP-1 RA group (no discontinuations); Five of nine patients in the FRC group discontinued due to TEAEs in the gastrointestinal disorder system organ class (SOC). The majority of patients across both treatment groups had TEAEs that were considered as mild or moderate in intensity.

Table 12 - Overview of adverse event profile: treatment-emergent adverse events during the 26-week randomized treatment period in Study EFC13794

n (%)	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Patients with any TEAE	163 (63.9%)	121 (47.3%)
Patients with any serious TEAE	10 (3.9%)	9 (3.5%)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	9 (3.5%)	0

TEAE: Treatment-emergent adverse event
n (%) = number and percentage of patients with at least one TEAE

The following TEAEs at the SOC level were reported more frequently in the FRC group compared with the GLP-1 RA group: gastrointestinal disorders, nervous system disorders, general disorders and administration site conditions, metabolism and nutrition disorders, and investigations. The most commonly reported TEAEs were nasopharyngitis (9.8% of patients in the FRC group versus 9.0% of patients in the GLP-1 RA group), nausea (8.6% and 2.3%, respectively) and diarrhoea (5.5% and 2.3%, respectively) ***Table*** .

Table 13 - Number (%) of patients experiencing common TEAE(s) (PT >=2% in any treatment group) by primary SOC and PT during the 26-week randomized treatment period

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Any TEAE	163 (63.9%)	121 (47.3%)
INFECTIONS AND INFESTATIONS	78 (30.6%)	68 (26.6%)
Bronchitis	6 (2.4%)	5 (2.0%)
Influenza	11 (4.3%)	6 (2.3%)
Nasopharyngitis	25 (9.8%)	23 (9.0%)
Pneumonia	6 (2.4%)	3 (1.2%)
Sinusitis	6 (2.4%)	7 (2.7%)
Upper respiratory tract infection	9 (3.5%)	12 (4.7%)
Urinary tract infection	7 (2.7%)	3 (1.2%)
METABOLISM AND NUTRITION DISORDERS	13 (5.1%)	1 (0.4%)
Increased appetite	6 (2.4%)	0
NERVOUS SYSTEM DISORDERS	30 (11.8%)	13 (5.1%)
Dizziness	6 (2.4%)	2 (0.8%)
Headache	10 (3.9%)	6 (2.3%)
GASTROINTESTINAL DISORDERS	55 (21.6%)	26 (10.2%)
Diarrhoea	14 (5.5%)	6 (2.3%)
Nausea	22 (8.6%)	6 (2.3%)
Toothache	6 (2.4%)	3 (1.2%)
Vomiting	8 (3.1%)	2 (0.8%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	23 (9.0%)	18 (7.0%)
Back pain	4 (1.6%)	7 (2.7%)
INVESTIGATIONS	15 (5.9%)	4 (1.6%)
Weight increased	7 (2.7%)	0

TEAE: Treatment-emergent adverse event, SOC: System Organ Class, PT: Preferred Term.
MedDRA version: 21.0.
n (%) = number and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and PT by alphabetic order.
Only SOC with at least one PT ≥ 2% in at least one group are presented.

Serious adverse events and deaths

During the 26-week randomized treatment period, no patient died or experienced TEAE leading to death (***Table*** 12). The percentage of patients who had at least 1 serious TEAE was similar between the treatment groups (3.9% in the FRC group and 3.5% in the GLP-1 RA group), and there were no significant differences between the treatment groups regarding the type of events reported. The serious TEAE of fall was reported in 2 patients (0.8%) in the FRC group (both events unrelated to hypoglycaemia), and all other SAEs were reported in no more than 1 patient in either treatment group.

None of the serious TEAEs were considered by the Investigator as possibly related to drug except for an event of hypoglycaemic unconsciousness in the FRC group.

Adverse events of special interest

Symptomatic hypoglycaemia

During the 26-week treatment period, 84 patients (32.9%) in the FRC group experienced at least one symptomatic hypoglycaemic event compared to 11 patients (4.3%) in the GLP-1 RA group (***Table 14***). The corresponding numbers of events per patient-year were 2.03 and 0.13, respectively. There were no symptomatic hypoglycaemic events leading to treatment discontinuation.

Furthermore, more patients in the FRC group experienced at least 1 documented symptomatic hypoglycaemic event with plasma glucose ≤3.9 mmol/L (≤70 mg/dL) (71 patients [27.8%]) compared to 6 patients (2.3%) GLP-1 RA group).

There was a single severe symptomatic hypoglycaemic event, reported in the FRC group. This event (preferred term [PT]: Hypoglycaemic unconsciousness) was also assessed as an SAE.

Table 14 - Summary of symptomatic hypoglycaemia recorded on the dedicated eCRF page and meeting protocol definition during the 26-week on-treatment period in Study EFC13794

	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Total patient years of exposure	121.4	127.0
Symptomatic hypoglycemia		
Number of patients with events, n (%)	84 (32.9%)	11 (4.3%)
Number of patients with events per patient year [a]	0.69	0.09
Number of events	246	17
Number of events per patient year [b]	2.03	0.13
Documented symptomatic hypoglycemia (plasma glucose ≤3.9 mmol/L [70 mg/dL])		
Number of patients with events, n (%)	71 (27.8%)	6 (2.3%)
Number of patients with events per patient year [a]	0.58	0.05
Number of events	187	10
Number of events per patient year [b]	1.54	0.08
Documented symptomatic hypoglycemia (plasma glucose <3.3 mmol/L [60 mg/dL])		
Number of patients with events, n (%)	41 (16.1%)	1 (0.4%)
Number of patients with events per patient year [a]	0.34	<0.01
Number of events	69	2
Number of events per patient year [b]	0.57	0.02

Documented symptomatic hypoglycemia (plasma glucose <3.0 mmol/L [54 mg/dL])			
Number of patients with events, n (%)	24	(9.4%)	1 (0.4%)
Number of patients with events per patient year [a]	0.20		<0.01
Number of events	30		1
Number of events per patient year [b]	0.25		<0.01
Probable symptomatic hypoglycemia			
Number of patients with events, n (%)	16	(6.3%)	1 (0.4%)
Number of patients with events per patient year [a]	0.13		<0.01
Number of events	27		1
Number of events per patient year [b]	0.22		<0.01
Severe symptomatic hypoglycemia			
Number of patients with events, n (%)	1	(0.4%)	0
Number of patients with events per patient year [a]	<0.01		0
Number of events	1		0
Number of events per patient year [b]	<0.01		0

a Calculated as number of patients with events divided by total exposure + 1 day in patient years for daily formulation and number of patients with events divided by total exposure + 7 days in patient years for weekly formulation .

b Calculated as number of events divided by total exposure + 1 day in patient years for daily formulation and number of events divided by total exposure + 7 day in patient years for weekly formulation .

Symptomatic hypoglycemia = symptomatic hypoglycemia recorded on the dedicated eCRF and meeting protocol definition for severe, or documented, or probable symptomatic hypoglycemia.
The 26-week on-treatment period is defined as the time from the first injection of investigational medicinal product (IMP) up to 1 day after the last injection of daily IMP (7 days after the last injection of weekly IMP) for patients not eligible to enter the extension period or Visit 28/Week 26 (or Day 183 if Visit 28/Week 26 is missing) for patients eligible to enter the extension period, regardless of the introduction of rescue therapy.

Adverse events related to injection site reactions

The incidence of any injection site reactions was 2.0% (n=5) in the FRC group and no patients in the GLP-1 RA group reporting an event. None of the injection site reaction TEAEs were serious, had a severe intensity or led to permanent treatment discontinuation.

Allergic/hypersensitivity events

Two events (occurring in 2 patients) were adjudicated as allergic reactions by the ARAC: Urticaria (hives), originally reported as "allergic reaction to nitrofurantoin mono-mcr" (PT: drug hypersensitivity) and asthma, originally reported as "worsening/relapse of seasonal allergies" (PT: seasonal allergy). Neither event was assessed as related to drug by the ARAC. No allergic reaction was reported in the GLP-1 RA group.

Pancreatic events

Per protocol, any increase in amylase and/or lipase >2 x ULN that had been confirmed by a repeat measurement was to be monitored and documented on a specific AE form and its associated complementary forms to be sent to an independent PSAC for adjudication.

During the first 26-week on-treatment period, the rate of TEAEs reported was similar in the FRC group and GLP-1 RA group (6 patients in each group; 2.4%, respectively). All events were sent to PSAC for adjudication of pancreatitis. There was a single positively adjudicated pancreatic event: one patient in the FRC group had pancreatic enzymes increase that was adjudicated by the PSAC as chronic pancreatitis not related to the IMP.

Pancreatic neoplasm related events were searched for based on a coding list of high-level terms (HLTs) and PTs related to pancreas, as well as using the Standardized Medical Dictionary for Regulatory Activities

(MedDRA) Query (SMQ) Malignancies and by searching for the term "pancreas" among PTs. No event was sent to PSAC for adjudication of pancreatic neoplasm.

Device-related events (DREs)

The percentage of patients with events reported on the DRE questionnaire was higher in the FRC group (21 patients [8.2%]) compared with the GLP-1 RA group (5 patients [2.0%]). None of the events were associated with a clinical event (i.e., symptomatic hypoglycaemia or any other AE)

Immunological events

Anti-insulin glargine antibodies

During the study, the anti-insulin antibody (AIA) status and concentrations were studied. The percentage of AIA positive patients increased from 2.1% (3 of 144 patients) at baseline to 17.4% (39 of 224 patients) at Week 26. The median AIA titer value did remained stable at Week 26 as compared to baseline.

The percentage of patients experiencing at least 1 TEAE was similar in AIA positive patients (67.5%) and AIA negative patients (64.9%). The number of documented symptomatic hypoglycaemic events with plasma glucose ≤3.9 mmol/L (≤70 mg/dL) per patient year was similar in AIA positive patients (1.34) and AIA negative patients (1.60).

In patients with positive AIA status, the percentage of patients with antibodies cross-reacting with human insulin was 100% (3 of 3 patients) at baseline and 94.7% (36 of 38 patients) at Week 26.

Anti-lixisenatide antibodies

The percentage of Anti-lixisenatide (ADA) positive patients increased from 16.8% (24 of 143 patients) at baseline to 44.5% (98 of 220 patients) at Week 26. At baseline, 7 of the 24 ADA positive patients had quantifiable ADA concentrations (median 16.13 nmol/L), and one of these patients had an ADA concentration above 100 nmol/L. At Week 26, 29 of the 98 ADA positive patients had quantifiable ADA concentrations (median 22.04 nmol/L), and 7 of these patients had ADA concentrations above 100 nmol/L.

The percentage of patients experiencing at least 1 TEAE was similar in ADA positive patients (67.2%) and ADA negative patients (63.2%). The number of documented symptomatic hypoglycaemic events with plasma glucose ≤3.9 mmol/L (≤70 mg/dL) per patient year was similar in ADA positive patients (1.43) and ADA negative patients (1.58)

The percentage of patients with antibodies cross-reacting with GLP-1 was 0% at baseline (0 of 24 patients) and 4.1% (4 of 98 patients) at Week 26. The percentage of patients with antibodies cross-reacting with glucagon was 4.2% at baseline (1 of 24 patients) and 2.0% (2 of 98 patients) at Week 26.

Laboratory findings

Lipids

There were no relevant differences between the two treatment groups and no relevant changes in either treatment group from baseline value to last on-treatment value for total cholesterol and high-density lipoprotein (HDL)-cholesterol. Change from baseline in triglycerides differed between the two treatment groups: median change from baseline to Week 26 was -13.67% in the FRC group and 1.75% in the GLP-1 RA group. Change from baseline in low-density lipoprotein (LDL)-cholesterol differed between the two treatment groups: median change from baseline to Week 26 was 7.12% in the FRC group and 2.18% in the GLP-1 RA group.

Pancreatic enzymes

Mean lipase and amylase values remained relatively constant throughout the study with no relevant increases in the FRC group versus the GLP-1 RA. The percentage of patients with at least 1 lipase value ≥3 x ULN during the first 26-week on-treatment period was low in both treatment groups with no relevant difference between the treatment groups (2.0% and 2.4% for the FRC and GLP-1 RA group, respectively). One patient (0.4%) in the FRC group and no patients in the GLP-1 RA group reported at least 1 amylase value ≥3 x ULN.

Calcitonin

Calcitonin values ≥20 and <50 ng/L were reported in 1 patient (0.4%) in the FRC group and 1 patient (0.4%) in the GLP-1 RA group; although, none of these values were confirmed by a repeat measurement. No patients had a serum calcitonin value ≥50 ng/L (pg/mL).

Electrolytes

There was no relevant change from baseline value in either treatment group for electrolytes (sodium, potassium, calcium, phosphorus).

Liver function

There was one TEAE of confirmed ALT increase (>3 x ULN), reported in 1 patient (0.4%) in the FRC group. The event was not serious, did not lead to treatment discontinuation and was not considered as possibly related to the drug by the Investigator.

No patients had ALT >5 x ULN in either treatment group. One patient (0.4%) in each treatment group had ALT >3 x ULN; however, no subject had a value that met Hy's law criteria.

Renal function

The percentage of patients with mild or moderate renal impairment during the first 26-week on-treatment period was similar between the treatment groups. No severe renal impairment or end stage renal disease was reported. Two patients (0.8%) in each treatment group had creatinine values ≥150 µmol/L (1.70 mg/dL). The number of patients with a creatinine value of ≥30% change from baseline was low with no relevant differences between treatment groups. The percentage of patients with post-baseline uric acid values >408 µmol/L (6.858 mg/dL) was similar between the treatment groups.

Vital signs

During the study period, there were small changes from baseline in sitting systolic blood pressure, diastolic blood pressure, and heart rate with no relevant differences between the treatment groups. The percentages of patients with PCSAs for blood pressure and heart rate during the first 26-week on-treatment period was low and similar between the treatment groups. Systolic blood pressure ≥160 mmHg and increase from baseline ≥20 mmHg was reported in 4.4% of patients in the FRC group and 2.7% of patients in the GLP-1 RA group. Diastolic blood pressure ≥110 mmHg and increase from baseline ≥10 mmHg was reported in 1 patient in the GLP1-RA group.

No heart rate ≥120 bpm and increase from baseline ≥20 bpm was reported in any patients.

Use in pregnancy

Pregnancy

One pregnancy was reported in a woman randomized in the FRC group. She had her last menstrual period on Day 74 of the study, and pregnancy was detected on Day 127. The IMP was permanently

discontinued with the last dose administered on Day 126. On Day 343, the patient delivered a healthy baby via caesarean section.

Another pregnancy started during the pre-treatment period and was detected in the blood sample taken on Day 1 of the study. However, before the results were received and the patient contacted, she was exposed to IMP for 7 days during her pregnancy. Her glycemia was not well controlled at screening as indicated by the screening HbA1c value (8.9%). She had a history of miscarriage. The last menstrual period was on Day -30 of the study. The IMP and metformin were permanently discontinued with the last dose administered on Day 7 for FRC and Day 8 for metformin. On Day 62, the patient had a missed abortion (PT: abortion missed). Pregnancy was terminated on Day 64 with no complications, and the patient recovered.

Both events of pregnancies were assessed as not related to the IMP by the both Investigator and the Sponsor.

Overdose

No TEAEs of symptomatic overdose was reported during the first 26-week on-treatment period.

Safety in special populations

Age

In the current study, no relevant differences in the proportion of patients reporting TEAEs by age group (<50 years, ≥50 to <65 years, ≥65 to <75 years, ≥75 years) were identified in either treatment group (range: 59.5% to 66.7% in the FRC group and 44.6% to 66.7% in the GLP-1 RA group).

In the FRC group, the highest number of documented symptomatic hypoglycaemic events (plasma glucose ≤3.9 mmol/L [≤70 mg/dL]) per patient year was observed in the ≥65 to <75 years age group (2.05 events per patient year versus 1.37 in the ≥50 to <65 years age group and 1.19 in the <50 years age group; the comparison is not meaningful for the ≥75 years age group because of the small number of patients [N=21]; of note, no patients reported such events in this group). In the GLP-1 RA group, the numbers of events per patient year were low and similar in all age groups (between 0 and 0.13 events per patient year).

The numbers of documented symptomatic hypoglycaemic events (plasma glucose ≤3.9 mmol/L [≤70 mg/dL]) were similar across age groups (between 1.4 and 1.6 events per patient year).

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

During the 26-week randomized treatment period, TEAEs leading to permanent treatment discontinuation were reported in 9 (3.5%) patients in the FRC group versus none in the GLP-1 RA group (**Table 15**). The most common TEAEs leading to permanent treatment discontinuation were nausea (3 patients [1.2%]) and weight increased (2 patients [0.8%]). All other PTs were reported only for 1 patient in the FRC group. None of the TEAEs leading to permanent treatment discontinuation were serious.

Table 15 Number (%) of patients experiencing TEAE(s) leading to permanent treatment discontinuation by primary SOC and PT during the 26-week randomized treatment period – Safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Fixed Ratio Combination (n=255)	GLP-1 Receptor Agonist (n=256)
Any TAE	9 (3.5%)	0
Nervous system disorders	1 (0.4%)	0
Headache	1 (0.4%)	0
Cardiac disorders	1 (0.4%)	0
Palpitations	1 (0.4%)	0
Gastrointestinal disorders	5 (2.0%)	0
Abdominal distension	1 (0.4%)	0
Flatulence	1 (0.4%)	0
Nausea	3 (1.2%)	0
Vomiting	1 (0.4%)	0
Pregnancy, puerperium and perinatal conditions	1 (0.4%)	0
Pregnancy	1 (0.4%)	0
General disorders and administration site conditions	1 (0.4%)	0
Fatigue	1 (0.4%)	
Investigations	4 (1.6%)	
Amylase increased	1 (0.4%)	0
Blood glucose fluctation	1 (0.4%)	0
Lipase increased	1 (0.4%)	0
Platelet count decreased	1 (0.4%)	0
Weight increased	2 (0.8%)	0

Post-marketing experience

The FRC has not been approved for the treatment of T2DM in patients not sufficiently controlled on OAD therapy and GLP-1 RA therapy. Therefore, no post-marketing data is available for this patient population.

Safety data from supportive studies

Study EFC14112

Overview of safety did not reveal differences between SGLT2i users and non-users. Regarding common treatment-emergent adverse events (TEAEs), TEAEs in the gastrointestinal disorder System Organ Class

(SOC) were reported less frequently in the FRC treatment group in SGLT2i users when compared to the SGLT2i non-users (17.6% versus 32.3%, respectively). Similarly, documented symptomatic hypoglycaemia (plasma glucose ≤3.9 mmol/L [≤70 mg/dL]) in the FRC group tended to be reported less frequently in SGLT2i users compared to non-users (number of events per patient year: 0.18 and 1.14, respectively).

Study EFC14114

Overview of safety did not reveal differences between SGLT2i users and non-users. Regarding common TEAEs, TEAEs in the gastrointestinal SOC were also reported numerically less frequently in the FRC group in SGLT2i users when compared to SGLT2i non-users (22.0% versus 27.4%, respectively). Documented symptomatic hypoglycaemia (plasma glucose ≤3.9 mmol/L [≤70 mg/dL]) was reported in similar proportions of SGLT2i users and non-users.

2.5.1. Discussion on clinical safety

The safety population from Study EFC13794 consisted of all randomized patients who received at least 1 dose of open-label fixed ratio combination of insulin glargine/lixisenatide (FRC) or GLP-1 receptor agonist (albiglutide, exenatide, dulaglutide or liraglutide). Of the 257 randomized patients in each treatment group, 90% completed the study in the FRC group and 96% in the GLP-1 RA group. The most common reason for IMP discontinuation were AEs and other reasons (not caused by adverse events, hypoglycaemia, lack of efficacy or poor compliance to protocol) in the FRC group (3.9% and 4.7%, respectively).

The percentage of patients who had at least 1 TEAE was higher in the FRC group than in the GLP-1 RA group (64% vs. 47%). Most patients across both treatment groups had TEAEs that were considered as mild or moderate in intensity.

The most frequently reported TEAEs were nasopharyngitis (9.8% and 9.0%), nausea (8.6% and 2.3%), and diarrhoea (5.5% and 2.3%) in the FRC and the GLP-1 RA groups, respectively, which are expected and labelled events for Suliqua. In the initial MAA, nausea was reported in 10% of FRC-treated patients, in line with the observed rate in the current study.

The percentage of patients who permanently discontinued drug due to a TEAE was overall low with a higher percentage of patients in the FRC group (3.5%) compared with the GLP-1 RA group (no discontinuations). The majority of patients (5 of 9) in the FRC group discontinued due to events of gastrointestinal disorders. GI events occurred shortly after initiation of FRC, which is not expected in this population as all patients in the FRC group had been transferred from a GLP1-RA. The imbalance in GI events between groups could however be explained by the fact that patients continuing GLP-1 RA treatment were shown to be tolerant to this therapy. Different GLP-1 RA may have a slightly different AE profile related to their pharmacokinetics, e.g. the mode of action of lixisenatide (predominantly post-prandial) is slightly different from other GLP1-RAs used as background medication (e.g. a longer-acting compounds). Indeed, 54.5% of the patients were treated with liraglutide, 20% with dulaglutide and 18.1% with exenatide extended-release. However, the percentage of patients who discontinued treatment due to GI AEs remains low (2%).

Similar numbers of serious TEAEs were reported in the FRC group (10 patients [3.9%]) and in the GLP-1 RA group (9 patients [3.5%]). None of the events were assessed as related with drug intake, except for one SAE of severe hypoglycaemia in the FRC group. No deaths occurred in either study group during the trial.

As expected, the frequency of symptomatic hypoglycaemia was higher (33% in the FRC group as compared to the GLP1-RA group (4.3%). That was even the case for documented symptomatic

hypoglycaemic events with plasma glucose ≤3.9 mmol/L (≤70 mg/dL) (28% compared to 2.3%) and ≤3.0 mmol/L (≤54 mg/dL) (9.4% compared to 0.4%). The higher rate of hypoglycaemia in the FCR group is concomitant with the addition of insulin treatment, as expected. Only one episode of severe hypoglycaemia (FRC group) was reported during the study.

The incidence of any injection site reactions was 2.0% (n=5; all non-serious) in the FRC group and no event in the GLP-1 RA group.

Two events of allergic reactions (urticaria and asthma) were reported in two patients in the FRC group and no events in the GLP-1 RA group. Both events were adjudicated as not related to the drug.

One FRC-treated patient reported a pancreatic TEAE; however, adjudicated as a chronic pancreatitis and not related to FRC.

The incidence of pancreatic neoplasm was and adverse event of 'special interest'. No pancreatic neoplasm was reported in either treatment group; however, the risk for developing malignancies cannot be fully explored in this study with a rather short observation period.

The incidence of device-related events (such as device performance failure, confusing instructions or use error difficulty) was higher in the FRC-group (8.2%) compared with the GLP-1 RA group (2.0%). This difference may be explained by the fact that patients in the GLP1-RA group continued with the same injection device they were familiar to prior to the inclusion in the study. However, none of the events were associated with a clinical event (i.e. symptomatic hypoglycaemic event, hyperglycaemic AE or any other AE).

During 26 weeks of treatment, the percentage of AIA (anti-insulin antibodies)-positive patients increased from 2.1% to 17% and ADA (anti-lixisenatide antibodies)-positive patients from 17% to 45%. In the FRC group, there was no substantial difference in the TEAE profile or documented symptomatic hypoglycaemia incidence between the antibody-positive and antibody-negative populations. In particular, there was no indication of any impact of antibody status on allergic reactions. The 5 cases of injection site reactions occurred in ADA-positive patients. However, the small number and the nature of reported events precluded any meaningful conclusion from the summaries of events by the ADA status. Low percentages (<5%) of patients with positive ADA status and having a cross-reactivity assessment had antibodies cross-reacting with GLP-1 or glucagon.

Change from baseline in triglycerides was -14% in the FRC group and 1.8% in the GLP-1 RA group. Change from baseline in low-density lipoprotein (LDL)-cholesterol was 7.1% in the FRC group and 2.2% in the GLP-1 RA group. Improvement in LDL and triglycerides in the FRC group is most likely related to the improvement in glucose metabolism. Lipase values ≥3xULN increased similar in the FRC group (2.0%) and GLP-1 RA group (2.4%); and amylase values ≥3 x ULN was reported in one patient (0.4%) in the FRC group and in no patients in the GLP-1 RA group.

Two pregnancies were reported during the study and the treatment was immediately discontinued according to the study protocol. Suliqua should not be used during pregnancy, as stated in section 4.6 of the SmPC. No relevant differences in the proportion of patients reporting TEAEs by age group (<50 years, ≥50 to <65 years, ≥65 to <75 years, ≥75 years) were identified in either treatment group (range: 59.5% to 66.7% in the FRC group and 44.6% to 66.7% in the GLP-1 RA group). Based on the current available data, Suliqua can be used in elderly patients, although experience of use in patients ≥75 years of age is limited.

Overall, the FRC was well tolerated during the 26-week treatment period. The safety profile of the FRC group generally reflected those of its components, and no new or unexpected safety signals were identified.

2.5.2. Conclusions on clinical safety

The safety profile for the fixed combination of lixisenatide/insulin glargine in Study EFC13794 is similar to that of its components and in line with previous phase 3 studies. As with other GLP1-RAs, gastrointestinal side effects remain the most common AE. The higher rate of hypoglycaemia in the insulin naïve FRC group is concomitant with the addition of insulin treatment, as expected. Only one episode of severe hypoglycaemia was reported in the FRC group. The study provides limited safety data on the concomitant use of Suliqua and pioglitazone and/or SGLT2i in addition to metformin. No new safety concerns were identified from the analysis of AEs reported in Study EFC13794. Gastrointestinal events, injection site reactions and urticaria are labelled and expected events for Suliqua.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version 4.1 with this application. The RMP was updated in line with GVP V rev 2. No new safety concerns were identified.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Pancreatitis
Important potential risks	Malignant neoplasm Pancreatic cancer Medullary thyroid cancer Medication errors including mix-ups between the different strength of the product
Missing information	Use in patients with severe renal impairment (with or without low body weight)

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
SULIQUA				
Survey to evaluate the knowledge and understanding of the key safety messages	To assess the knowledge and understanding of the key safety	Medication errors including mix-ups between the	Study completion	31-Jul-2020 4Q 2020

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
in the healthcare professional guide and the patient guide for SULIQUA Planned, with protocol to be submitted 6 months post-approval	messages in the HCP and patient guides among HCPs who prescribed or dispensed SULIQUA and patients treated with SULIQUA, respectively.	different strength of the product	Final study report	
Pharmacoepidemiology study: Patient registry of lixisenatide use in adult type 2 diabetes Ongoing	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 Lombardia region (Italy) and in Belgium.	Acute pancreatitis, pancreatic cancer, and thyroid cancer, in particular medullary thyroid cancer.	Final report	Q1 2021
Insulin glargine				
None				
GLP-1: Glucagon-Like Peptide-1; $HbA1_c$: Glycosylated Hemoglobin; HCP: Healthcare Professional; Q: Quarter; SGLT2: Sodium-Glucose Co-Transporter 2; T2DM: Type 2 Diabetes Mellitus.				

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Pancreatitis	**Routine risk minimization measures:** Addressed in SmPC section 4.4 (Special warnings and precautions for use); PIL	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	section 2 (What do you need to know before you use Suliqua) Prescription only medicine **Additional risk minimization measures:** None	None **Additional pharmacovigilance activities:** Lixisenatide individual component Pharmacoepidemiology program: • A patient registry to monitor the occurrences of the acute pancreatitis, pancreatic and thyroid cancer events in lixisenatide-treated patients after launch.
Important potential risks		
Malignant neoplasm	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Pancreatic cancer	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Lixisenatide individual component Pharmacoepidemiology program: • A patient registry to monitor the occurrences of the acute pancreatitis, pancreatic and thyroid cancer events in lixisenatide-treated patients after launch.
Medullary thyroid cancer	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None	None **Additional pharmacovigilance activities:** Lixisenatide individual component Pharmacoepidemiology program: • A patient registry to monitor the occurrences of the acute pancreatitis, pancreatic and thyroid cancer events in lixisenatide-treated patients after launch.
Medication errors including mix ups between the different strength of the product	**Routine risk minimization measures:** **<u>1- Mix-up between long acting (basal) and short acting (bolus) insulin, including by visually impaired or color blind patients</u>** PIL section 2 (What do you need to know before you use Suliqua) SmPC section 4.4 (Special warnings and precautions for use) and section 6.6 (Special precautions for disposal and other handling) Packaging: V The packaging displays high differentiation in color and presentation from other compound V Safety message "for single patient use only" prevents sharing treatment with other patients. Prescription only medicine **<u>2- Mix-up between different Suliqua strengths, including by visually impaired or color blind patients</u>** SmPC section 4.2 (Posology) and section 4.4 (Avoidance of medication errors) PIL section 3 (How to use Suliqua) Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Survey to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide for SULIQUA.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	3- Non-compliance with instructions for use SmPC section 4.2 (Posology and method of administration) PIL section 3 (How to use Suliqua) **4- Misuse related to extraction of insulin from the pre-filled pen using a syringe** SmPC section 4.2 (Posology and method of administration) and section 4.4 (Avoidance of medication errors) Proposed text in IFU: "**Never use a syringe to remove medicine from your pen**. If you do you, may not get the correct amount of medicine." **5- Non-compliance with instructions to use a new needle for each injection** SmPC section 4.2 (Posology and method of administration) and section 6.6 (Special precautions for disposal and other handling) PIL section 3 (How to use Suliqua) Proposed text in IFU: ""**Never re-use needles.** If you do, you might not get your full dose (underdosing) or get too much (overdosing) as the needle could block." Packaging: The outer carton and label of the prefilled pen include the statement that the product should only be used in the prefilled pen. The outer carton and label include the statement "Always use a new needle". The carton displays a prominent warning about misuse related to extraction of "Suliqua®" from the prefilled pen using a syringe.	

Safety concern	Risk minimization measures	Pharmacovigilance activities
	<u>6- Switching error: from conventional insulin to Suliqua and vice versa</u> SmPC section 2 (Qualitative and quantitative composition) SmPC section 4.2 (Posology and method of administration) PIL section 3 (How to use Suliqua) The use of an adequate pen differentiation after the trade name is needed to identify the two different pens of Suliqua and minimize the risk of medication errors between the two pen strengths. The final packaging contains the amount of each active ingredient on the package. It also provides the range of insulin glargine that each pen provides. The dose range of each pen 10-40 or 30-60 is noted after the trade name in the SmPC, the PIL and the IFU and presented as highlight on the outer packaging and the pen label. The expression of the name of the medicine is displayed as: "SULIQUA® SoloStar® insulin glARGine 100 units/ml + 50 micrograms/ml lixisenatide solution for injection in a pre-filled pen, 10-40 dose steps (1 dose step = 1 unit of insulin glARGine + 0.5 micrograms of lixisenatide)" The outer carton includes description of the content of a dose step in the main field of view such that it can be clearly seen. Definition of the dose step only for the type of pen contained (100/33 or 100/50) and not for both pen types; The word "Suliqua" more prominent than "SoloStar".	

Safety concern	Risk minimization measures	Pharmacovigilance activities
	For the outer carton and pen labels, color of pen and packaging are aligned. Prescription only medicine **Additional risk minimization measures:** HCP guide and Patient guide	
Missing information		
Use in patients with severe renal impairment (with or without low body weight)	**Routine risk minimization measures:** Addressed in SmPC section 4.2 (Posology and method of administration); section 4.4 (Special warning and precautions for use); section 5.2 (Pharmacokinetic properties); PIL section 2 (What do you need to know before you use Suliqua) and section 3 (How to use Suliqua) Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

HCP: Healthcare Professional; IFU: Instructions for Use; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance.

In addition, the MAH took the opportunity to update the contact details of the local representatives in Denmark, the Netherlands and Malta in the Package Leaflet and to implement minor editorial changes in the annexes.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Suliqua is the fixed ratio combination (FRC) of the GLP-1 RA lixisenatide and the basal insulin glargine. Lixisenatide is currently approved for the treatment of adult patients with T2DM. Insulin glargine is used in both type 1 and type 2 diabetes patients.

The currently applied indication for Suliqua is;

"Suliqua is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to metformin and/or SGLT-2 inhibitors. (For study results with respect to effects on glycaemic control, and the populations studied, see Section 4.4 and 5.1)."

3.1.1. Disease or condition

Due to the pathophysiology of the disease, the majority of T2DM patients require more treatment as the disease progresses and beta-cell function declines over time. A poly-pharmaceutical approach is often preferred in order to achieve good metabolic control. The aim of the current variation application is to investigate the feasibility of switching patients inadequately controlled on treatment with GLP1-RAs (on top of OADs) to the FRC. Both GLP1-RAs and insulin are administered as subcutaneous injections. Based on the results of a new study, the MAH proposed changes to several sections of the SmPC, including the wording of the indication.

3.1.2. Main clinical studies

Study EFC13794 was designed to assess the efficacy and safety of the FRC Suliqua (insulin glargine and lixisenatide) in patients with T2DM who were inadequately controlled with GLP-1 RAs in combination with OADs. Patients randomised to Suliqua continued their background OAD treatment throughout the study.

The study had a 1:1 randomized, active-controlled, 2-arm, 26-week treatment duration, parallel group, multinational and multi-center Phase 3b design. It included 514 patients with T2DM inadequately controlled with daily or weekly GLP-1 RAs combined with metformin with or without pioglitazone and/or an SGLT-2 inhibitor. The inclusion and exclusion criteria were adequate and reflect the proposed target population. The study appears adequately conducted. The subject population included in the study was representative of the expected target population.

3.2. Favourable effects

The study met the primary objective. The change in HbA1c was greater with Suliqua when compared to unchanged GLP1-RA therapy (LS mean difference: -0.64%; 95% CI: -0.770 to -0.508; p <0.0001). HbA1c decreased on average -1.02% in the FRC group and -0.38% in the GLP-1 RA group.

All studied secondary endpoints support the primary outcome. The percentage of patients reaching HbA1c <7% was significantly higher in the FRC group (61.9%) compared with the GLP-1 RA group (25.7%). The reduction in fasting plasma glucose was significantly greater in the FRC group (-2.28 mmol/L) compared to the GLP-1 RA group (-0.6 mmol/L). The mean plasma glucose values at all time points in the 7-point SMPG profiles were lower in the FRC group compared to the GLP-1 RA group. Treatment with the FRC improved postprandial glycaemic control after a standardized liquid breakfast in comparison to GLP-1 RA

(-3.96 mmol/L [-71.32 mg/dL] in the FRC group and -1.11 mmol/L [-19.99 mg/dL] in the GLP-1 RA group. There was a greater reduction from baseline in 2-hour plasma glucose excursion for the FRC compared to GLP-1 RA: -1.51 mmol/L (-27.20 mg/dL) in the FRC group and -0.52 mmol/L (-9.40 mg/dL) in the GLP-1 RA group.

The percentage of patients who required rescue therapy was lower in the FRC group (4.8%) compared to the GLP-1 RA group (15.0%), with a risk difference of -10.00% (95% CI: -14.93%, -5.06%).

To support the proposed extension of the indication to concomitant treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i), data for a total of 115 patients treated simultaneously with SGLT2i and FRC in clinical trials (including data on 93 patients included in Japanese Phase 3 trials) have been provided. The outcome with regard to change in HbA1c was consistent across the different studies and comparable with the outcome for the overall study populations as previously described.

3.3. Uncertainties and limitations about favourable effects

Of the 12 patients requiring rescue therapy in the FRC group, 11 had reached the 60 U dose. This fact demonstrates that some patients require a higher insulin dose than what can be managed by use of the FRC.

3.4. Unfavourable effects

The safety profile for the fixed combination of lixisenatide/insulin glargine in Study EFC13794 is similar to that of its components and in line with previous experience from FRC insulin glargine/lixisenatide clinical studies.

The frequency of patients who had at least 1 TEAE was 64% in the FRC group and 47% in the GLP-1 RA group. Most of the events were mild to moderate in intensity. The incidence of serious TEAEs was 3.9% in the FRC group and 3.5% in the GLP-1 RA group; however, none of the events were assessed as related, except for one SAE of severe hypoglycaemia in the FRC group. No deaths occurred in either study group during the trial.

Nine patients (3.5%) discontinued permanently in the FRC group and no patients discontinued in the GLP-1 RA group. Most patients (5 of 9) in the FRC group discontinued due to events of gastrointestinal disorders.

The incidence of symptomatic hypoglycaemia was 33% in the FRC group and 4.3% the GLP1-RA group and the incidence of documented symptomatic hypoglycaemia (≤3.9 mmol/L) was 28% and 2.3% for the FRC group and GLP-1 RA group, respectively.

Events of any injection site reactions were frequently more common in the FRC group (2.0%; all non-serious) than in the GLP-1 RA group (no event).

Two events of allergic reactions (urticaria and asthma) were reported in two patients in the FRC group and no events in the GLP-1 RA group. Both events were adjudicated as of not related to the drug.

One FRC-treated patient reported a pancreatic TEAE; however, adjudicated as a chronic pancreatitis and not related to FRC.

During treatment, the incidence of AIA (anti-insulin antibodies)-positive patients increased from 2.1% to 17% and ADA (anti-lixisenatide antibodies)-positive patients from 17% to 45%.

The incidence of device-related events (such as device performance failure, confusing instructions or use error difficulty) was higher in the FRC-group (8.2%) compared with the GLP-1 RA group (2.0%).

However, none of the events were associated with a clinical event (i.e. symptomatic hypoglycaemic event, hyperglycaemic AE or any other AE).

Lipase values ≥3xULN increased similarly in the FRC group (2.0%) and GLP-1 RA group (2.4%). Amylase values ≥3 x ULN was reported in one patient (0.4%) in the FRC group and in no patients in the GLP-1 RA group.

No relevant differences in the proportion of patients reporting TEAEs by age group were identified in either treatment group.

To support the proposed extension of the indication to concomitant treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i), data for a total of 115 patients treated simultaneously with SGLT2i and FRC in clinical trials (including data on 93 patients included in Japanese Phase 3 trials) have been provided. No safety concerns arise from the assessment of the safety data from these studies.

3.5. Uncertainties and limitations about unfavourable effects

In summary, the safety profile of fixed combination of lixisenatide/insulin glargine is in line with findings from previous studies and no new safety concerns arise.

3.6. Effects Table

Table 16 Effects Table for Suliqua in T2DM patients inadequately controlled on GLP1-RA and OADs (data cut-off: 09 July 2018)

Effect	Short description	Unit	Suliqua	GLP1-RA	Uncertainties / Strength of evidence	References
Favourable Effects						
HbA1c	Change from baseline to week 26	%	-1.02	-0.38	LS mean difference (SE) -0.64 (0.067)	EFC13794
2-hours PPG excursion	Change in 2-hour PPG and in blood glucose excursion during standardized meal test from baseline to Week 26	mmol/L	-3.96	-1.11	-2.85 (0.290)	EFC13794
Body weight	Change from baseline to week 26	kg	1.89	-1.14	LS Mean difference (SE) 3.03 (0.312)	EFC13794
HbA1c < 7%	Percentage of patients reaching HbA1c <7% (53 mmol/mol) at Week 26	%	61.9	25.7	Proportion difference (%) 36.05	EFC13794
Unfavourable Effects						
Documented symptomatic Hypoglycaemia	Plasma glucose ≤3.9 mmol/L	%	27.8	2.3		EFC13794
GI events	Reported AEs on a SOC level	%	21.6	10.2		EFC13794

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The change in HbA1c achieved by changing from GLP1-RA to Suliqua is clinically relevant and in line with other studies. The effect is similar across genders, age groups, ethnicity, independent of HbA1c or BMI at baseline. The study population was treated with a wide range of GLP1-RA, both short- and long-acting, supporting the validity of this treatment strategy. More patients in the FRC-group reached a level of HbA1c recommended by international health authorities in the field of diabetes, which in turn may result in fewer secondary complications.

The observed increase in body weight is expected after the initiation of insulin treatment. As beta-cell function declines, insulin treatment may be the most suitable therapeutic option. The achievement of good metabolic control outweighs the possible consequences of increased body weight in this patient population.

Suliqua is currently approved 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. The restriction to combination with metformin is due to the fact that all other OADs, as well as basal insulin, were discontinued at baseline in the pivotal studies supporting the initial MAA.

With the current application, the MAH initially proposed to extend the indication to include concomitant treatment with other OADs than metformin ("*as an adjunct to diet and exercise in addition to other oral medicinal products for the treatment of diabetes*"). As this was not accepted by the CHMP due to a lack of, or very limited data, on the combination with other OADs than metformin, the MAH proposed during the procedure to include concomitant treatment with metformin and/or SGLT2i ("*as an adjunct to diet and exercise in addition to metformin and/or SGLT-2 inhibitors*"). The data supporting the extension to include the simultaneous use of SGLT2i is provided by study EFC13794, where 26 patients (10,1%) were treated with the FRC and SGLT2i. Further, the MAH has provided supplementary data from 93 patients treated with SGLT2i and FRC included in Japanese Phase 3 trials (34 patients (21.1%) from study EFC14112 and 59 patients (22.7%) from Study EFC14114). The data from the clinical trials, albeit limited, are considered to support the efficacy and safety of the combination with SGLT2i. However, for clarity the final wording was amended as follows: "*as an adjunct to diet and exercise in addition to metformin ~~and/or~~* ***with or without*** *SGLT-2 inhibitors*"

3.7.2. Balance of benefits and risks

T2DM is a progressive disease, eventually leading to beta-cell burnout and the need for insulin replacement therapy. As the disease progresses, polypharmacy is inevitable, challenging compliance. Introduction of basal insulin therapy by means of the FRC offers a simple step towards improved metabolic control in this patient population, without the addition of a second subcutaneous injection. While body weight increases after the initiation of insulin treatment, this effect may be ameliorated by the concomitant use of GLP1-RA. Having a GLP1-RA with a post-prandial profile may even delay the need of prandial insulin. Hypoglycaemia remains a cornerstone of insulin treatment, especially prandial insulin. Postponing the initiation of prandial insulin may indeed limit the total risk for hypoglycaemia in this patient group.

The current study shows that patients inadequately controlled with GLP1-RA on top of metformin may benefit from a change to the FRC Suliqua, achieving a better metabolic control, although being at risk of getting more hypoglycaemias and increasing in body weight. The FRC may improve compliance by

combining two drugs in the same subcutaneous injection. Therefore, the benefit-risk balance is considered positive in patients inadequately controlled with GLP1-RA.

Limited efficacy and safety data from clinical trials have been provided to support the proposed extension of the indication to include concomitant treatment with metformin with or without SGLT-2 inhibitors, which are considered to support an extension of the indication to "*in addition to metformin **with or without** SGLT-2 inhibitors*".

3.7.3. Additional considerations on the benefit-risk balance

An extension of the indication should preferably be supported/explained in section 5.1 of the SmPC and the MAH has proposed the following wording, which is considered acceptable:

> *Concomitant use of Suliqua with SGLT-2 inhibitors (SGLT2i)*
>
> *The concomitant use of Suliqua with SGLT2i is supported by subgroup analyses from three Phase 3 randomized clinical trials (119 patients on the insulin glargine/lixisenatide fixed ratio combination (FRC) who also received SGLT2i).*
>
> *One study conducted in Europe and North America included data from 26 patients (10.1%) who concomitantly received insulin glargine/lixisenatide FRC, metformin and an SGLT2i. Two more Phase 3 studies from the dedicated Japanese clinical development program performed in patients not reaching sufficient glycaemic control on OADs provided data for 59 patients (22.7%) and 34 patients (21.1%), respectively, who concomitantly received SGLT2i and insulin glargine/lixisenatide FRC.*
>
> *The data from these 3 studies show that initiation of Suliqua in patients inadequately controlled with a treatment including SGLT2i leads to improved change in HbA1c versus the comparators. There was no increased risk of hypoglycemia and no relevant differences in the overall safety profile in SGLT2i users compared to non-users*.

3.8. Conclusions

The overall B/R of Suliqua in *"the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to metformin with or without SGLT-2 inhibitors"* is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to include "treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to metformin with or without SGLT-2 inhibitors" based on the phase 3 Study EFC13794; a 26-week randomized, open-label, active controlled, parallel-group, study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with Type 2 Diabetes inadequately controlled on GLP-1 receptor agonist and metformin (alone or with pioglitazone and/or SGLT-2 inhibitors), followed by a fixed ratio combination single-arm 26-week extension period.

As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the contact details of the local representatives in Denmark, the Netherlands and Malta in the Package Leaflet and to implement minor editorial changes in the annexes. An updated RMP version 4.1 was agreed during the procedure.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan are recommended.