Non-interventional study report

Study ID: NN2211-4077

Retrospective collection of effectiveness and safety data from patients treated with liraglutide or DPP-4 inhibitor in primary care in Europe

A Retrospective Epidemiological Study

PASS Information

Title	Retrospective collection of effectiveness and safety data from type 2 diabetes patients treated with liraglutide or DPP-4 inhibitor in primary care in Europe: A retrospective epidemiological study
Version identifier of the final study report	1.0
Date of last version of the final study report	Not applicable
EU PAS register number	ENCEPP/SDPP/8135
Active substance	Pharmacotherapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excl. insulins. ATC code: A10BX07 (Liraglutide). Dipeptidyl peptidase 4 (DPP-4) inhibitors (A10BH).
Medicinal product	Victoza® (Liraglutide, NNC 90-1170) 6 mg/ml solution for injection in pre-filled pen. DPP-4 inhibitors (according to license)
Product reference	Liraglutide (Victoza®): EMEA/H/C/001026
Procedure number	EMEA/H/C/001026
Marketing authorisation holder(s)	Novo Nordisk A/S
Joint PASS	No
Research question and objectives	Primary objective(s): • To demonstrate the clinical effectiveness, safety and place in clinical practice of liraglutide and DPP-4 inhibitor therapy in routine primary care across Europe Secondary objective(s): • Assess the direct resource utilisation of liraglutide and DPP-4 inhibitor therapy in primary care • Illustrate the health economic value of liraglutide compared with DPP-4 inhibitor therapy in routine primary care • Assess HCPs perception of the utility of liraglutide in relation to DPP-4 inhibitor therapy in routine primary care • Assess impact of mode of administration on therapy initiation in routine primary care • Evaluate perceived patient acceptability of liraglutide in relation to DPP-4 inhibitor therapy in routine primary care
Countries of study	France, Germany, Spain, and the United Kingdom
Author	Dr. [redacted] [redacted], Novo Nordisk Health Care AG, Thurgauerstrasse 36, CH-8050 Zurich, Switzerland

Marketing authorisation holder(s)

Marketing authorisation holder(s) **(MAH(s))**	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
MAH contact person	Dr. [redacted] Novo Nordisk Health Care AG Thurgauerstrasse 36 CH-8050 Zurich Switzerland

Universal trial number (UTN)	Universal Trial Number (UTN): U1111-1142-2764 ClinicalTrials.gov identifier: NCT01890993
IND number	Not applicable
EudraCT number	Not applicable
Japanese study number	Not applicable
Generic name	Liraglutide
Indication	Victoza® contains the medicinal ingredient liraglutide which is an analogue of human glucagon-like peptide-1 (GLP-1). Victoza® is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.[1]
Investigator(s)	One principal investigator was appointed at each of the 78 study sites in the study. The following investigator was designated signatory investigator for the study and was responsible for reviewing and approving the study report: • [redacted] The following were designated coordinating investigator(s) for each country in which the study was performed: • Dr. [redacted]; Dr [redacted]; Dr. [redacted]; and Dr [redacted]
Study initiated	First patient first study visit is not applicable as this study was retrospective. The following represents the date of first patient recruited per country: France: 07 Dec 2013 Germany: 17 Sep 2013 Spain: 09 Jan 2014 UK: 06 Aug 2013
Study completed	France: 06 June 2014 Germany: 11 Dec 2013 Spain: 06 June 2014 UK: 31 Mar 2014

Lead study manager	[redacted]
Study manager(s)	Not applicable
Epidemiologist	[redacted]

This study was conducted in accordance with the Declaration of Helsinki amended at the 64th World Medical Association (WMA) General Assembly, Fortaleza, Brazil, October (2013)[2], and the Guidelines for Good Pharmacoepidemiology Practices.

Table of contents

List of in-text figures

Page

List of in-text tables

Page

1 Abstract

Please refer to separate document

2 List of abbreviations and definitions of terms

2.1 Abbreviations

AE	adverse event
ANOVA	analysis of variance
CI	confidence interval
Coef	coefficient
CRO	contract research organisation
DPP-4	dipeptidyl peptidase-4
eCRF	electronic case report form
FE	fixed effects
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
GP	general practitioner
GPP	guidelines for good pharmacoepidemiology practices
HbA_{1c}	glycated haemoglobin A1c
HCP	health care professional
IC	informed consent
ICF	informed consent form
IHD	ischaemic heart disease
Meg	meglitinide
Met	metformin
MI	myocardial infarction
PVD	peripheral vascular disease
PYE	patient-years of exposure
QALY	quality-adjusted life year
RCT	randomised controlled trial
RE	random effects
SAE	serious adverse event
SBP	systolic blood pressure
SMBG	self-monitoring of blood glucose
SD	standard deviation
SE	standard error
SU	sulphonylurea
T2DM	type 2 diabetes mellitus
TX	treatment
TZD	thiazolidinedione
VAS	visual analogue scale

2.2 Definition of terms

In this document 'Physician' refers to the individual overall responsible for the conduct of the study at a study site.

In this document, 'DPP-4 inhibitor' therapy refers to treatment with any dipeptidyl peptidase-4 (DPP-4) inhibitor.

3 Investigators

There were 78 principal investigators in the study – one appointed at each of the 78 study sites in the study, investigator details are provided in Appendix 1, see Annex 1. The following investigator was designated signatory investigator for the study and was responsible for reviewing and approving the study report:

- [redacted]

The following were designated coordinating investigator(s) for each country in which the study was performed:

- Dr. [redacted]
- Dr [redacted]
- Dr. [redacted]
- Dr [redacted]

4 Other responsible parties

Novo Nordisk UK contracted with contract research organisation [redacted], who selected the sites, collected and compiled all data.

Data management and database hosting was delegated to Professor [redacted] After completed study report the data will be transferred to Novo Nordisk Ltd. who owns the data

Novo Nordisk UK contracted with Professor [redacted] for statistical analysis plan and statistical analyses.

5 Milestones

Planned and actual dates for study milestones are summarised in Table 5–1.

Table 5–1 Milestones

Milestone	Planned date	Actual data	Comment
France			.
Start of data collection	07 Dec 2013	07 Dec 2013	Not applicable
End of data collection	06 Jun 2014	06 Jun 2014	Not applicable
Germany			
Start of data collection	17 Sep 2013	17 Sep 2013	Not applicable
End of data collection	11 Dec 2013	11 Dec 2013	Not applicable
Spain			
Start of data collection	09 Jan 2014	09 Jan 2014	Not applicable
End of data collection	06 Jun 2014	06 Jun 2014	Not applicable
United Kingdom			
Start of data collection	06 Aug 2013	06 Aug 2013	Not applicable
End of data collection	31 Mar 2014	31 Mar 2014	Not applicable
Registration in the EU PAS register	27-Feb-2014	27-Feb-2014	Not applicable
Final report of study results	06 Jun 2015	06 Jun 2015	Not applicable

On 02 June 2014, Novo Nordisk confirmed that recruitment and study should be stopped in France and Spain due to difficulties in recruiting the initially planned number of subjects in the Primary Care settings. Data collection was completed 06 June 2014

6 Rationale and background

6.1 Background

Type 2 diabetes mellitus (T2DM), previously referred to as non-insulin-dependent diabetes, or adult onset diabetes, is a chronic, progressive and complex metabolic disorder characterised by hyperglycaemia arising from a combination of relative insulin deficiency, due to an inadequate insulin secretory response, together with peripheral resistance to insulin action. Commonly associated with elevated blood pressure and abnormal lipid levels, those with T2DM are at an increased risk of developing macrovascular (cerebrovascular, coronary and peripheral vascular disease) and microvascular (retinopathy, neuropathy and nephropathy) complications.[3]

The initial treatment for T2DM is typically a combination of metformin and lifestyle (diet and exercise) modifications. When metformin and lifestyle changes become insufficient T2DM patients may be escalated onto further treatment options such as sulphonylureas (SUs), pioglitazone, or insulin. However SUs and insulin are often complicated by weight gain and/or hypoglycaemia.[4]

In clinical trials the addition of incretin-based therapies, such as glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs) and dipeptidyl peptidiase-4 (DPP-4) inhibitors, to existing oral therapies has been shown to improve glycaemic efficacy without weight gain (weight loss for GLP-1-RA), and with low hypoglycaemia incidence, mostly reported when used concomitantly with SUs.[1, 5-8] Head-to-head studies of up to 12 months duration show that patients taking GLP-1RAs demonstrate greater glycaemic control and result in greater weight loss compared with the DPP-4 inhibitor sitagliptin (Januvia®).[9-12] Furthermore, patient reported outcome measures showed an improvement in treatment satisfaction with the GLP-1RA liraglutide (Victoza®) 1.8 mg versus sitagliptin 100 mg, as add on to metformin; patient reported treatment satisfaction was comparable for liraglutide 1.2 mg versus sitagliptin 100 mg.[13]

Liraglutide is licenced in Europe for the treatment of T2DM to achieve glycaemic control in combination with oral glucose-lowering therapies, and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.[1] The majority of patients requiring treatment augmentation following metformin are routinely managed in primary care; however evidence suggests that the majority of liraglutide initiation currently tends to occur in specialist care, despite appropriate reimbursement. By contrast DPP-4 inhibitor therapy initiation may more commonly occur in a primary care setting. There is therefore an evidence gap pertaining to the appropriate use and outcomes associated with liraglutide prescribing in a primary care setting given that prescribing decisions are typically based on evidence collected from clinical trials conducted in secondary care settings which may not reflect primary care management and outcomes.

6.2 Rationale for the study

More robust and extensive data reflecting the role of incretin-based therapies in primary care across Europe is sought after by both clinicians and payers. There is therefore a clear rational to conduct an

retrospective primary care based cohort study of liraglutide in relation to DPP-4 inhibitor therapy across multiple European countries.

6.3 Benefit-risk balance

Liraglutide has demonstrated a clinically relevant effect on glycaemic control in patients with type 2 diabetes if used in combination with sulphonylurea, with metformin, with metformin and thiazolidinedione or with metformin and sulphonylurea.[14-19] In these combinations the benefit/risk ratio for liraglutide is considered positive.[20]

Major hypoglycaemia (low blood glucose) may occur uncommonly and has primarily been observed when liraglutide is combined with a sulphonylurea (0.02 events/patient year).[1] Very few episodes (0.001 events/patient year) were observed with administration of liraglutide in combination with oral antidiabetics other than sulphonylureas.[1] The risk of hypoglycaemia is low with combined use of basal insulin and liraglutide (1.0 events/patient year).[1] Other very common side effects (that may affect more than 1 patient in 10) are nausea and diarrhoea, which are both transient in nature and usually subside over time.[1] This study sought to determine the safety and tolerability profile of liraglutide in the primary care setting by asking HCPs to record patient experience of adverse events and tolerability issues, as well as diabetes-related complications which included the recording of hypoglycaemia.

6.4 Ethics

This study was conducted in accordance with the Declaration of Helsinki amended at the 64th World Medical Association (WMA) General Assembly, Fortaleza, Brazil, October (2013)[2], and the Guidelines for Good Pharmacoepidemiology Practices and regulatory requirements as stated in the protocol.

The study was approved by authorities and committees in each respective country according to local regulation before any study procedures. Local ethics submission was conducted by Contract Research Organization (CRO): [redacted].

In the context of retrospective data collection, Local ethic committees (LEC) for France, Germany and the UK accepted a waiver for informed consent (IC) on the basis that all data was anonymised and as there was no direct patient contact. Spain was the only country where an informed consent form (ICF) was required. The ICF was designed quality controlled by [redacted]. In Spain, the information was given to the patient during a phone call with the physician who sent the ICF for signature. Data was collected once the signed ICF was collected from the patient. Instructions on ICF obtaining process were given to the physicians in a written document.

Confidentiality of patients' information was ensured by the collection of anonymous data since patients were identified by a unique number, their age and gender only. No direct monitoring of individual data was conducted and no nominative information/documentation was collected.

7 Research question and objectives

As stated in the protocol, the objectives of the study were as follows:

Primary objective:

- To demonstrate the clinical effectiveness, safety, and place in clinical practice, of liraglutide and DPP-4 inhibitor therapy in routine primary care across Europe.

Secondary objective:

- Assess the direct resource utilisation of liraglutide and DPP-4 inhibitor therapy in primary care
- Illustrate the health economic value of liraglutide compared with DPP-4 inhibitor therapy in routine primary care.
- Assess health care professionals (HCPs) perception of the utility of liraglutide in relation to DPP-4 inhibitor therapy in routine primary care.
- Assess impact of mode of administration on therapy initiation in routine primary care.
- Evaluate perceived patient acceptability of liraglutide in relation to DPP-4 inhibitor therapy in routine primary care.

Note: The evaluation did not differentiate between treatments in terms of or type of DPP-4 inhibitor. Subjects were co-prescribed oral concomitant therapies, including metformin, SUs, TZDs, and meglitinide; however, the analysis did not evaluate specific dual and triple therapy combinations.

8 Amendments and updates

The initial study protocol version 2.6 was amended as described in Table 8–1, and is included at Appendix 2a. The amended protocol version 2.7, 28 November, 2013, is included as Appendix 2b, see Annex 1.

There were no amendments made to the study protocol after the start of data collection.

Table 8–1 Amendments to the protocol

Number	Title	Date	Section of study protocol	Reason
1.	Amendment Protocol Version 2.7	28-Nov-2013	1. Summary 3.2 Outcome variable 5. Study population 7. Methods and assessments 12. Statistical considerations 13. Ethics	Extension of the data collection at month 12 from ±2 months to -3/+6 months; clarifications and corrections of study processes

9 Research methods

9.1 Study design

A retrospective study of primary care based liraglutide and DPP-4 inhibitor therapy was conducted across four European countries: France, Germany, Spain and the United Kingdom (UK). Anonymised patient level data was collected by the subjects' own general practitioner and an electronic case report form (eCRF) was used to capture the data. In order to minimize potential reporting and prescribing bias and to ensure face validity of the study, data was collected from consecutive subjects on either liraglutide or a DPP-4 inhibitor over a similar time frame, at least 6 months after initial product launch within each country. Further, Novo Nordisk was not directly involved in site selection. An external CRO, [redacted], selected the sites, collected and compiled all data.

The analysis was entirely retrospective in nature and did not involve direct patient contact. Baseline, 3, 6 and 12-month treatment data was collected on subjects initiated on and completing at least 12 months of treatment with liraglutide or a DPP-4 inhibitor in primary care or primarily managed in primary care. Only data from subjects initiated on liraglutide or a DPP-4 inhibitor within approved EMA licensed indications was collected. To assist Novo Nordisk with interpretation of study findings and with publication of results in each country, a local diabetes specialist and a local primary care physician from each country was appointed by Novo Nordisk to participate in a multinational steering committee. Each such individual had a willingness to engage with local primary care physicians and participate in publication of the study findings

9.2 Setting

A retrospective study of primary care based liraglutide and DPP-4 inhibitor therapy was conducted across 78 study sites in 4 European countries: France, Germany, Spain and the UK. Anonymised patient level data was collected by the subjects' own general practitioner between and 07 December 2013 and 06 June 2014 depending on country, see Section 5, Table 5–1. A list of investigators is provided as Appendix 1, see Annex 1.

An eCRF was used to capture the data. A copy of the eCRF is provided as Appendix 3, see Annex 1. An external CRO: [redacted] selected the sites, collected and compiled all data. See Section 9.3.5 for further details on patient selection.

The study considered subjects initiated with liraglutide or DPP-4 inhibitor therapy. The evaluation did not differentiate between treatments dose and type of DPP-4 inhibitor. Subjects were co-prescribed oral concomitant therapies, including metformin, SUs, TZDs, and meglitinide; however, the analysis did not evaluate specific dual and triple therapy combinations.

9.2.1 Case report forms

[redacted] provided a system for Electronic Data Capture, and ensured that all relevant questions were answered and that no empty data blocks existed. A copy of the Novo Nordisk and [redacted] had no direct access to patient records. Data were collected and anonymised by the subjects´ own general practitioners. By signing the affirmation statement electronically, the physician confirmed that the information was completed and corrected. A copy of the eCRF is provided as Appendix 3, see Annex 1.

9.3 Subjects

Consecutive subjects with T2DM initiated with liraglutide or a DPP-4 inhibitor and primarily managed in primary care with 12 (-3/+6, i.e. 9 to 18) months of available data were included in this study. Subjects were excluded if they had received either liraglutide or DPP-4 inhibitor therapy prior to being initiated with liraglutide or DPP-4 inhibitor therapy in this study.

Only data derived from subjects receiving either therapy in accordance with licensed indications were included and analysed. Anonymised patient level data was collected by the subjects' own general practitioners. There was no direct patient contact.

The primary time points for data collection were baseline (anytime within 6 months before therapy initiation) and at 12 (-3/+6, i.e. 9 to 18) months.

9.3.1 Inclusion criteria

Subjects treated with liraglutide or DPP-4 inhibitors, according to license in respective participating country, with data available for 12 (-3/+6, i.e. 9 to 18) months.

9.3.2 Exclusion criteria

Subjects treated with liraglutide or DPP-4 inhibitors, outside of license in respective participating country.

Subjects with a prior treatment history of liraglutide or DPP-4 inhibitors were excluded.

9.3.3 Removal of subjects from therapy or assessment

Not applicable. The study was retrospective in nature.

9.3.4 Sources of subjects

[redacted] selected the sites, collected and compiled all data. Patient data was collected from patient charts.

9.3.5 Methods of selection of subjects

Data from eligible subjects was collected from 78 study sites across four countries (France, Germany, Spain and the UK). In order to facilitate identification of suitable sites by [redacted], Novo Nordisk, where possible and relevant, supplied [redacted] with information on local primary care formulary status for liraglutide and information about local primary care prescription density by geographical area. Novo Nordisk was not directly involved in site selection process in order to avoid site selection bias.

9.4 Variables

9.4.1 Primary effectiveness variables

- Change in HbA_{1c} after 12 (-3/+6, i.e. 9 to 18) months

9.4.2 Key secondary effectiveness variables

- Change in systolic blood pressure (SBP) after 12 (-3/+6, i.e. 9 to 18) months.
- Change in body weight after 12 (-3/+6, i.e. 9 to 18) months.

9.4.3 Other secondary variables

- Change in other effectiveness variables: diastolic blood pressure (DBP), waist circumference, body mass index (BMI), and pulse rate.
- Changes in resource utilisation: GP visits, test strip use, secondary care visits, concomitant glucose lowering medications and changes in anti-hypertensive and cholesterol-lowering therapies
- Safety and diabetes related complications.
- HCP perceptions of liraglutide and DPP-4 inhibitor therapy and factors determining therapy choice as assessed by HCP.

9.5 Data sources and measurement

9.5.1 Data collection time points

Data was collected during baseline (anytime within 6 months before therapy initiation) and at following time points after therapy initiation: 3 (±1), 6 (±1) and 12 (-3/+6, i.e. 9 to 18). The 12 month time point was the primary time point for data analysis. As the study was retrospective in nature, and as data availability at 3 (±1) and 6 (±1) months was not an inclusion criteria, it was not expected that all subjects would have all data for 3 (±1) and 6 (±1) month time points.

9.5.1.1 Assessments for safety and effectiveness

Baseline data collection

Baseline (anytime within 6 months before therapy initiation) patient demographic data was collected to provide information in relation to:

- Age
- Gender
- Recorded duration of diabetes
- Current medication (anti-hypertensive and lipid lowering therapy use)
- HbA_{1c}
- Body weight (or Body Mass Index [BMI])
- Body height
- Waist circumference
- Blood pressure
- Test strip (self-monitoring blood glucose [SMBG]) prescriptions over last 6 months (in countries where strips are prescribed and the data is therefore available)
- Number of GP visits over last 6 months
- Number of secondary care visits over last 6 months
- Complications / Comorbidities

When recording the baseline data the primary HCPs were also asked to identify the most important factor determining therapy choice (liraglutide or DPP-4 inhibitor) - if this was remembered: The question asked was as follows:

1. Which of the following was the main factor that drove your decision towards initiating drug X (liraglutide or DPP-4 inhibitor) for this patient?
    A. Mode of administration
    B. Patient acceptance/preference
    C. Glucose lowering efficacy
    D. Potential to achieve HbA_{1c} target
    E. Effects on body weight
    F. Combination of glucose and weight lowering effects
    G. Cost

Three, six and twelve month data collection

Data was collected for the time points 3 (±1), 6 (±1) and 12 (-3/+6, i.e. 9 to 18) months following therapy initiation to reflect:

- Change in HbA_{1c}
- Any changes in concomitant blood glucose lowering therapy

- Change in body weight (or BMI)
- Change in waist circumference
- Change in blood pressure
- Information about antihypertensive and lipid lowering therapy use (12 months only)
- Number of prescribed test strips (in countries where this information was collected)
- Number of GP visits, in-patient visits and hospitalizations
- Number of secondary care visits
- Any change in complication status
- Safety and tolerability data

When recording the 12 (-3/+6, i.e. 9 to 18) month observations, data reflecting qualitative endpoints assessing primary HCP perceptions of liraglutide and DPP-4 inhibitor therapy were collected by means of series of questions using a linear 10 point visual analogue scale (VAS) scale - if this was remembered: The questions asked were as follows:

1. For you as a GP, how difficult was it to initiate and maintain this patient on drug X?
   10 extremely easy – 0 extremely difficult
2. For the patient, how big of an issue is the mode of administration?
   10 No concern – 0 Extremely concerned
3. How satisfied is the patient with drug X?
   10 Extremely satisfied – 0 Extremely dissatisfied
4. How satisfied have you been with drug X in this patient?
   10 Extremely satisfied – 0 Extremely dissatisfied
5. How cost-effective do you think drug X has been for this patient?
   10 Extremely cost effective – 0 No health economic value

The questionnaire used was a non-validated questionnaire. This approach was taken to manage costs and timelines.

9.5.1.2 Reporting of safety information

Safety information (if previously reported) was captured in the eCRF. Clinicians were instructed to describe any adverse events, in the course of treatment, that were reported by the patient. There were two fields for data entry “did you report any Adverse Events to the authorities?” and “did the patient report any intolerability?” where the clinician could write a free text response.

This information was collected by the Novo Nordisk pharmacovigilance departments in the participating countries.

As the study was retrospective in nature it was not feasible, or appropriate, to make an assessment of causality and the medicinal products at individual case level. Also there was no requirement to

report the collected adverse events to health authorities in an on-going manner during the study, as the study makes secondary use of data.

9.6 Bias

In order to minimise potential reporting and prescribing bias, and to ensure face validity of the study, data was collected from consecutive subjects initiated on either liraglutide or a DPP-4 inhibitor over a similar time frame, at least 6 months after initial product launch within each study country. Further, Novo Nordisk was not directly involved in site selection; [redacted] selected the sites, and also collected and compiled all data.

9.7 Study size

Based on the currently available clinical trial and UK primary care pilot study data it was hypothesized that an extensive European routine primary care based study would demonstrate:

- Superior clinical efficacy of liraglutide compared with DPP-4 inhibitor therapy in routine primary care (a statistically significant 0.3% difference in HbA_{1c} with liraglutide vs. DPP-4 inhibitor therapy with a SD of 1.0%)
- Primary care health care professional acceptability of liraglutide
- Ease of initiation of liraglutide in primary care
- Neutral resource implication for liraglutide initiation in primary care
- Health economic benefits of liraglutide in routine primary care
- Good tolerability and patient acceptability of liraglutide in primary care

Using currently available UK pilot study data from primary care as a reference [21], power calculations were undertaken based on the requirement to demonstrate statistical significance within each country. A total of 174 subjects with 12-month data in each treatment arm for each country were found to be required in order to demonstrate a statistically significant 0.3% difference in HbA_{1c} with liraglutide versus DPP-4 inhibitor therapy, with a SD of 1.0%; a two-sided test was assumed, as the orientation of the observed difference in HbA_{1c} is not yet known.

Current UK study data suggests a rate of discontinuation within 12 months of up to 20% with liraglutide and DPP-4 inhibitor therapy.[21] After adjusting for this, a total of 220 patient cases in each treatment cohort needed to be screened in order to deliver approximately 174 treatment completers, as required to demonstrate a significant 0.3% HbA_{1c} difference between treatments.

A cap of 10 subjects per arm per site was applied, resulting in a total of 51 practices across all countries required, assuming a statistical power of 80%, and after incorporating the cluster design and fixing the number of observations that each cluster were required to recruit (a cap of 10 subjects per arm per cluster, equal to 20 subjects per cluster).

9.7.1 Power calculations

Power calculations were undertaken, based on the requirement to demonstrate statistical significance within each country. Table 9–1 illustrates the number of subjects with 12-month data required (completers) to demonstrate statistically ($p < 0.05$) significant 0.3% and 0.5% HbA_{1c} differences between treatment with liraglutide and treatment with DPP-4 inhibitor therapy for each country. Thus, in order to demonstrate a statistically significant 0.3% difference in HbA_{1c} with liraglutide vs. DPP-4 inhibitor therapy with a SD of 1.0% a total of 174 subjects in each treatment cohort with 12 month data will be required. We assume a two sided test as the orientation of the observed difference in HbA_{1c} is not yet known.

Table 9–1 Number of subjects with 12-month data required (completers) to demonstrate statistically ($p < 0.05$) significant 0.3% and 0.5% HbA_{1c} differences

	HbA_{1c} difference	
SD	**0.3% (n)**	**0.5% (n)**
0.5	45	17
1.0	174	64
1.5	394	143

Current UK study data suggests a discontinuation rate with liraglutide and DPP-4 inhibitor therapy within 12 months of up to 20%[21], hence in order to demonstrate a significant 0.3% HbA_{1c} superiority in favour of liraglutide a total of 220 patient cases in each treatment cohort will need to be screened in order to deliver approx. 174 treatment completers. A cap of 10 subjects per arm per site will be applied. [redacted] selected the sites.

Now, incorporating the cluster design and assuming a statistical power of 80%, the following sample sizes & number of clusters are required. Table 9–2 illustrates, after fixing the number of observations that each cluster will recruit (a cap of 10 subjects per arm per cluster, equal to 20 subjects per cluster), the minimum number of clusters and sample sizes required to detect a statistically significant ($p<0.05$) difference in HbA_{1c} of 0.3% (standard deviation 1.0%) across all countries.

Table 9–2 Sample size calculations with cluster design

Intra-class correlation	**HbA_{1c} treatment difference**	
	0.3% cluster (Sample size), n	**0.5% cluster (Sample size), n**
0.05	35 (342)	13 (123)
0.10	51 (508)	19 (183)
0.15	68 (674)	25 (243)

Thus, in order to demonstrate, across all countries, a statistically significant 0.3% difference in HbA_{1c} with liraglutide vs. DPP-4 inhibitor therapy with a SD of 1.0% a total of 51 practices are needed where, on average, 10 subjects finish treatment within each arm in each practice.

Summary:

Countries planned to participate: France, Germany, Spain and the UK.

Planned number of subjects to be screened: 220 subjects per arm per country.

Planned number of subjects to be included in the study: 174 subjects per arm per country

9.8 Data transformation

In order to ensure the data was reported in a usable format, a "cleaning" process was undertaken to remove missing and erroneous values and ensure consistency in reporting. Steps taken were consistently applied to each of the four datasets, and the values replaced for each are reported.

9.8.1 Approach to missing data

The following were replaced with "NA":

- Any value appearing as "-99" or "-1"
- "0" values for all clinical parameters

9.8.2 Approach to erroneous data

The following were replaced with "NA" if outside of the specified range:

- Age [< 18, > 100]
- HbA_{1c} (%) [< 4, > 14]
- HbA_{1c} (mmol/mol) [< 20, > 130]
- SBP [< 70, > 250]
- DBP [< 35, > 150]
- Waist circumference [< 50, > 250]
- Height [< 75, > 250]
- BMI [< 10, > 60]
- Weight [< 30, > 250]
- Heart rate [< 40, > 200]

9.8.3 HbA_{1c} reporting

HbA_{1c} values should have been consistently reported as percentages. If value was defined as a % but appeared to be mmol/mol value (defined as a value between 20 and 130), then the value was

converted. If value was defined as mmol/mol but appeared to be % (defined as a value between 4 and 14), then it was not converted.

Values were converted from IFCC mmol/mol to DCCT % using the following formula:

mmol/mol value/10.929 + 2.15

9.8.4 Approach to multiple values

For subjects with multiple measurements (per parameter), the measurement closet to the relative time point (i.e. 3 months from initiation, 6 months from initiation, etc.) was utilised. If the measurement corresponded to an "NA" value then the measurement from the next closest time point was utilised.

9.8.5 Approach to correct timeframe for observations

Only observations from subjects that adhered to the following rules were incorporated in the final dataset:

- The subjects' first recorded consultation date must have been within the six-month period prior to treatment initiation.
- The subjects' final consultation date (month 12) must have lay within 9 and 18 months after the treatment initiation date.

9.9 Statistical methods

9.9.1 Main summary measures

The primary analysis summarised subjects' baseline clinical and demographic profiles (N, mean, standard deviation). The statistical significance of between group differences in baseline characteristics was assessed using the Pearson's chi-squared test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Changes in study variables from baseline to 12 months were assessed using one-way ANOVA, with change as the dependant variable, and treatment group as the factor variable. Missing data were analysed for patterns and multiple imputation implemented to overcome loss of data due to incomplete records. Multivariate statistical models were fitted to the complete data.

9.9.2 Main statistical methods

Testing of treatment difference was undertaken using a linear mixed-effects model with treatments centres modelled as a random effect. Across all sites, multi-level modelling was extended to include centre and country effects. This analysis was adjusted for baseline demographic and risk factor profiles, concordant with the data collected as specified in the study protocol and described in Section 9.9.2.1.

9.9.2.1 Evaluating treatment difference

A linear mixed-effects model was used to assess treatment differences between liraglutide and DPP-4 inhibitor therapies. A linear mixed-effects model is a model that takes in to consideration variation that is not generalisable to the independent variables. Mixed-effects models were fitted to complete (multiple imputation, N=20) data sets generated by applying the NORM package in R [22]; NORM utilises an Expectation Maximisation algorithm for estimation of means, variances and co-variances of data and a data augmentation procedure for generating multiple imputations, as described by Schafer *et al.*[23] All multivariate analyses were undertaken in STATA version 11.2.[24] The following primary and key secondary outcomes were assessed:

- Change in HbA_{1c}
- Change in body weight
- Change in systolic blood pressure

Both centre and country were modelled as random effects, to account for variation within and across countries. The analysis was adjusted for baseline demographic and risk factor profiles concordant with the data collected, as specified in the study protocol.

The interaction between variables was investigated, and the significance of variables and their interactions was evaluated in order to improve the model fit. A general to specific selection methodology was applied to the data to estimate a reduced model for each analysis. The goodness of fit of each model was assessed using appropriate statistical tests (e.g. the Chi-square likelihood ratio test), with a p value less than 0.05 indicating significance for covariate selection (unless otherwise indicated).

An additional multivariate analysis was undertaken for the variables primary (GP visits) and secondary (hospitalisations) care utilisation. Adjusted linear mixed-effects models were fitted to the variables 'change in GP visits' and 'change in secondary care visits', with patient characteristics (fixed effects) and country and centre (random) effects. Models specification was as described for the evaluation of treatment difference.

Differences in the primary and key secondary variables (HbA_{1c}, weight, SBP) were also evaluated for the following subgroup (reason for treatment initiation with liraglutide or a DPP-4 inhibitor) in a descriptive analysis of the actual (non-imputed) data:

- Mode of administration
- Patient acceptance/preference
- Glucose lowering efficacy
- Potential to achieve HbA_{1c} % target
- Effects on body weight
- Combination of glucose and weight lowering effects

- Cost

9.9.3 Missing values

As this study was retrospective in nature and relied on data collection from already existing medical records, it was anticipated that not all subjects would have all measurements. Imputation is the act of filling in "missing values" with plausible estimates and is commonly applied within statistical analyses using a range of different methods. Imputation is used so as to attempt to avoid any problems or biases which can be caused by missing data. In this analysis, multiple imputation was used to estimate missing data.

9.9.3.1 Multiple imputation

Multiple imputation accounts for missing data by restoring natural variability in missing data and incorporating uncertainty caused by estimating missing data. The missing values in a dataset are estimated from correlated variables in the dataset to create an "imputed dataset". This process is carried out multiple times time to create multiple imputations. The uncertainty caused by estimating data is accounted for by the multiple imputations, whilst the variability of the missing data is accounted for by the individual, correlated, imputations. The imputed data sets are then combined using the following methods:

The mean dataset is estimated by taking the average of the imputed datasets:

$\bar{Q} = \frac{1}{n}\sum_{j=1}^{n} Q_j$ where Q_j is an estimate of a missing piece of data and n is the number of imputed datasets

In order to provide an estimate of the standard error (SE) of the combined imputations, a method was used, derived by Rubin 1987, where:

$\bar{U} = \frac{1}{n}\sum_{j=1}^{n} U_j$ is an estimate of the within-imputation variance where U_j is an estimate of the SE associated with Q_j,

$B = \frac{1}{n-1}\sum_{j=1}^{n}(Q_j - \bar{Q})^2$ is an estimate of the between-imputation variance;

And $T = \bar{U} + \left(1 + \frac{1}{n}\right) B$ is an estimate of the total variance.

Missing data was analysed for patterns and multiple imputations were implemented to overcome loss of data due to incomplete records.

9.9.4 Sensitivity analyses

A sensitivity analysis was undertaken reporting outcomes for all subjects involved in the study (N=952 subjects), excluding the approach of specifying an appropriate timeframe for observations for the study follow-up points (see Section 9.8.5).

9.9.5 Amendments to the statistical analysis plan

There were no amendments to the statistical analysis plan.

9.10 Quality control

The processes taken to remove missing and erroneous values and ensure consistency in reporting data are described in Section 9.8. Steps taken were consistently applied to each of the four datasets. Multiple imputation, as described in Section 9.9.3.1, was used to estimate any missing data.

10 Results

10.1 Participants

A retrospective study of primary care based liraglutide and DPP-4 inhibitor therapy was conducted across 4 European countries: France, Germany, Spain and the UK. Overall, anonymised subject level data was collected from 952 subjects across the four countries. Data was collected by the subjects' own general practitioner captured by an eCRF. The captured data underwent a "cleaning" process (as described in Section 9.8) in order to identify and remedy any inconsistencies, or multiple measurements, and create a succinct dataset for analysis purposes. After removing inconsistencies and multiple entries, data was available for all of the original 952 subjects.

- **Identified inconsistencies** included the incorporation of illogical values under certain observations: in total 22,261/197,064 values across all patients, all countries, were removed and 165 values were modified in line with the assumptions made in Section 9.8.

- **Multiple measurements** were observed at a patient level at observation time points (3-, 6- and 12-month observations); across subjects, there were 138 instances of multiple measurements and these were discarded (i.e. each subject contributed one row of data to the analysis dataset).

The final step in the data "cleaning" process involved removing subjects whose consultations did not lie within pre-specified time ranges for inclusion. Following this stage of cleaning, data relating to 264 subjects were excluded Figure 10–1; 688/952 (72%) of subjects were included in the final dataset for analysis and, among these subjects 23.92% of all possible observations were missing. The majority of missing values related to at 3 months and 6 month time points, and waist circumference was missing in the majority of subjects. Values for primary and key secondary effectiveness outcomes were well represented.

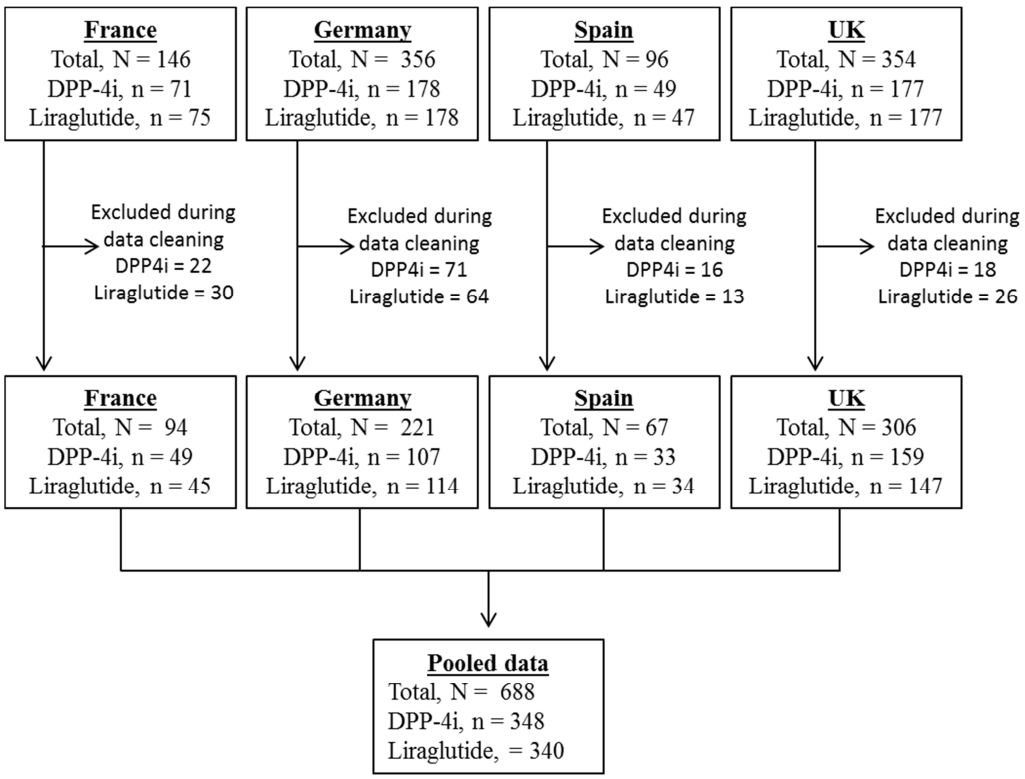

Figure 10–1 Subject disposition

10.2 Descriptive data

Following the data cleaning process, 688/952 (72%) subjects were included in the final dataset for analysis. The majority of subjects were from Germany and the UK (Germany: 221, UK: 306), with fewer subjects from France and Spain (France: 94, Spain: 67), as a result of premature termination of data collection as a consequence of poor recruitment at sites within these countries.

Baseline demographics were generally comparable across countries, but there were some significant differences in baseline demographics between subjects initiated with liraglutide and subjects initiated with DPP-4 inhibitors in some countries, Table 10–1. This included a male predominance for those initiated with liraglutide in the UK (63.9%), compared to a female predominance in Spain (67.6%).

The duration of diabetes prior to therapy initiation was longer for subjects in the UK (120 months [10 years] in DPP-4 inhibitor initiates, and 160 months [13.3 years] liraglutide initiates), and shorter in Germany 78.6 months [6.6 years] in DPP-4 inhibitor initiates, and 78.9 months [6.6 years] liraglutide initiates) compared to the pooled dataset (99.8 months [8.3 years] in DPP-4 inhibitor initiates and 120 months [10 years] in liraglutide initiates, Table 10–1.

In the pooled data from the four European countries there was a significant difference ($p<0.05$) between subjects initiated with liraglutide versus those initiated with a DPP-4 inhibitor at baseline for the following characteristics: age, HbA_{1c} levels, waist circumference, BMI and weight, Table 10–1 and Table 10–2. Mean age was lower in subjects initiated with liraglutide (59.9 years) versus those initiated with a DPP-4 inhibitor (64.6 years). Mean HbA_{1c}, waist circumference, BMI and weight were higher in those subjects initiated with liraglutide versus those initiated with a DPP-4 inhibitor. Analysed subjects in the UK dataset, particularly those initiated with liraglutide, had a higher HbA_{1c} level, waist circumference, BMI, weight and pulse rate compared to subjects in other countries, Table 10–2.

Table 10–1 Subject demographics at baseline, by country and pooled

Subject characteristics	Pooled		UK		France		Germany		Spain	
	DPP-4 inhibitor N=348	Liraglutide N=340	DPP-4 inhibitor N=159	Liraglutide N=147	DPP-4 inhibitor N=49	Liraglutide N=45	DPP-4 inhibitor N=107	Liraglutide N=114	DPP-4 inhibitor N=33	Liraglutide N=34
Subject demographics at baseline										
Age (years)	64.6 (11.0)	59.9 (10.0)	63.7 (11.2)	58.7 (10.3)	64.7 (12.1)	61.9 (9.29)	65.2 (10.5)	60.7 (10.2)	66.6 (9.04)	59.9 (9.20)
Gender										
Female, (%)	142 (40.8%)	158 (46.5%)	56 (35.2%)	53 (36.1%)	19 (38.8%)	22 (48.9%)	51 (47.7%)	60 (52.6%)	16 (48.5%)	23 (67.6%)
Male (%)	206 (59.2%)	182 (53.5%)	103 (64.8%)	94 (63.9%)	30 (61.2%)	23 (51.1%)	56 (52.3%)	54 (47.4%)	17 (51.5%)	11 (32.4%)
Height (cm)	168 (9.80)	170 (10.1)	169 (9.94)	171 (11.2)	167 (8.71)	168 (7.64)	170 (9.34)	171 (9.02)	162 (9.95)	161 (6.92)
Duration of diabetes, months [years]	99.8 (67.6) [8.3]	102 (63.9) [8.5]	120 (69.3) [10]	120 (67.4) [10]	80.7 (49.2) [6.7]	104 (65.3) [8.7]	78.6 (67.1) [6.6]	78.9 (54.1) [6.6]	99.8 (56.2) [8.3]	103 (53.4) [8.6]

SD: standard deviation.
Note: all data is mean (SD) unless otherwise indicated.

Table 10–2 Subject clinical measurements at baseline, by country and pooled

Subject characteristics	Pooled		UK		France		Germany		Spain	
	DPP-4 inhibitor N=348	Liraglutide N=340	DPP-4 inhibitor N=159	Liraglutide N=147	DPP-4 inhibitor N=49	Liraglutide N=45	DPP-4 inhibitor N=107	Liraglutide N=114	DPP-4 inhibitor N=33	Liraglutide N=34
Clinical measures at baseline										
HbA_{1c} (%)	8.22 (1.30)	8.81 (1.56)	8.44 (1.24)	9.40 (1.53)	8.05 (1.24)	8.38 (1.52)	7.92 (1.19)	8.16 (1.24)	8.38 (1.74)	9.01 (1.75)
SBP (mmHg)	137 (14.5)	139 (14.9)	137 (16.2)	140 (17.1)	135 (12.2)	136 (10.3)	139 (12.5)	139 (13.9)	136 (15.0)	137 (13.3)
DBP (mmHg)	78.6 (9.03)	79.9 (10.1)	77.4 (9.95)	80.4 (11.4)	76.3 (9.17)	75.5 (8.66)	81.9 (6.93)	81.3 (8.31)	77.0 (7.49)	78.5 (9.95)
WC (cm)	107 (13.5)	118 (15.0)	115 (18.6)	131 (14.3)	102 (8.31)	104 (9.50)	107 (11.2)	117 (12.7)	98.6 (10.5)	116 (11.8)
BMI (kg/m^2)	31.7 (5.87)	36.8 (6.85)	32.6 (6.69)	38.1 (7.15)	29.8 (4.76)	32.9 (6.38)	30.5 (4.23)	35.4 (6.50)	31.0 (4.30)	36.4 (4.70)
Weight (kg)	89.0 (19.3)	104 (22.5)	93.3 (20.9)	112 (23.7)	82.4 (19.6)	90.5 (16.9)	88.7 (17.0)	102 (20.5)	79.4 (9.72)	93.3 (15.2)
Pulse rate (bpm)	75.9 (9.96)	76.4 (9.35)	77.4 (10.5)	83.3 (5.99)	73.7 (9.18)	74.6 (9.86)	75.7 (9.44)	76.1 (9.37)	78.6 (12.1)	77.1 (8.67)

BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation; WC: waist circumference.
Note: all data is mean (SD) unless otherwise indicated.

10.3 Outcome data

See Table 10–3, Table 10–4 and Table 10–5 for the numbers of subjects by categories of main outcomes for the two treatment groups and the pooled data. Data were originally collected at baseline and at the time points 3 (±1), 6 (±1) and 12 (-3/+6, i.e. 9 to 18) months following therapy initiation. In Table 10–3 only data at baseline and 12 months is presented. Please refer to Appendix 4 for data at time points 3 and 6 months, see Annex 1.

Table 10–3 Numbers of subjects with effectiveness outcomes at baseline and 12 months: Pooled data and by treatment

	Pooled data	DPP-4 inhibitor	Liraglutide
Per protocol population (N)	**688**	**348**	**340**
Effectiveness outcome variables			
HbA_{1c} (%)			
Subjects with data at baseline	688	348	340
Subjects with data at 12 months	687	348	339
SBP (mmHg)			
Subjects with data at baseline	686	348	338
Subjects with data at 12 months	683	346	337
DBP (mmHg)			
Subjects with data at baseline	686	348	338
Subjects with data at 12 months	687	348	339
Waist circumference (cm)			
Subjects with data at baseline	177	80	97
Subjects with data at 12 months	185	92	93
BMI (kg/m^2)			
Subjects with data at baseline	501	257	244
Subjects with data at 12 months	493	259	234
Weight (kg)			
Subjects with data at baseline	677	343	334
Subjects with data at 12 months	674	341	333
Pulse rate (bpm)			
Subjects with data at baseline	373	190	183
Subjects with data at 12 months	389	200	189

BMI: body mass index; DBP: diastolic blood pressure; HbA_{1c}: haemoglobin A1c; SBP: systolic blood pressure; SD: standard deviation.

Table 10–4 Numbers of subjects with resource utilisation outcomes at baseline and 12 months: Pooled data and by treatment

	Pooled data	DPP-4 inhibitor	Liraglutide
Resource utilisation	**688**	**348**	**340**
Diabetes related GP visits			
Subjects with data at baseline	584	287	297
Subjects with data at 12 months	592	287	292
Total GP visits			
Subjects with data at baseline	587	296	291
Subjects with data at 12 months	596	306	290
Secondary care visits			
Subjects with data at baseline	412	201	211
Subjects with data at 12 months	373	188	185
SMBG test strip use			
Subjects with data at baseline	335	169	166
Subjects with data at 12 months	379	180	199
Subjects with data at 12 months	185	92	93
Subjects receiving concomitant blood glucose lowering therapy			
Subjects with data at baseline	629	318	311
Subjects with data at 12 months	634	321	313
Change in use of anti-hypertensive medications			
Subjects with data at baseline	589	296	293
Subjects with data at 12 months	598	301	297
Change in use of cholesterol-lowering medications			
Subjects with data at baseline	589	296	293
Subjects with data at 12 months	598	301	297

GP: general practitioner; SMBG: self-monitoring blood glucose

Table 10–5 Numbers of subjects with data for safety and diabetes related complications

	Pooled data	DPP-4 inhibitor	Liraglutide
Safety and diabetes-related complications	**688**	**348**	**340**
Safety			
Subjects with data at baseline	584	287	297
Diabetes-related complications			

Subjects with data	688	348	340

10.4 Main results

Retrospective collection of anonymised subject level data from medical records were collected via an eCRF completed by the subjects own GP. Due to the volume of data collected, the main results present analysis based on pooled data from the four European countries (France, Germany, Spain and the UK) at baseline and at 12 months, in line with key primary and secondary variables. An analysis of outcomes based on country-level data from each of the four European countries, including 3 month and 6 month time points are provided in Appendix 4, see Annex 1.

10.4.1 Primary effectiveness outcome (change in HbA_{1c})

The primary variable in determining effectiveness was change in glycaemic control assessed as the change in HbA_{1c} from baseline at 12 months (-3/+6, i.e. 9 to 18 months) following treatment initiation. The difference in HbA_{1c} was statistically significant between the liraglutide and DPP-4 inhibitor groups at baseline (8.81% and 8.22% respectively, $p<0.001$).

Overall 687 subjects (99.9% out of 688 per-protocol population (pooled data)) had primary effectiveness data for HbA_{1c} available at baseline and the 12 month time point Table 10–6. This comprised of all 348/348 (100%) subjects initiated with DPP-4 inhibitor and 339/340 (99.7%) subjects initiated with liraglutide.

Based on unadjusted univariate estimates there was a statistically significant reduction in HbA_{1c} of --0.21% ($p=0.042$) in those treated with liraglutide compared to DPP-4 inhibitors, from baseline at 12 months, Table 10–6.

For the outcome change in HbA_{1c} at 12 months, following adjustment for patient (fixed) and random effects, the estimated difference between the groups (mean, SE) was -0.19% (0.11) in favour of liraglutide ($p=0.072$). This estimate compared to a difference of -0.22% (0.10) in the mixed-effects intercept only model ($p=0.028$) and -0.21% in the analysis of the original data ($p=0.042$).

Table 10–6 Primary effectiveness variable: Change in HbA_{1c} from baseline at 12 months

	Overall	**DPP-4 inhibitor**	**Liraglutide**	**DPP-4 inhibitor vs. Liraglutide**
Per protocol population (N)	**688**	**348**	**340**	
Subject with data at baseline and 12 months	**687**	**348**	**339**	
HbA_{1c} measurement at baseline, Mean (SD)	8.51 (1.46)	8.22 (1.30)	8.81 (1.56)	<0.001

	Overall	DPP-4 inhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide
HbA_{1c} measurement at 12 months, Mean (SD)	7.64 (1.33)	7.45 (1.20)	7.83 (1.43)	<0.001
Change in HbA_{1c} (%) from baseline at 12 months				
Mean (SD)	-0.87 (1.36)	-0.77 (1.19)	-0.97 (1.51)	-0.21 (0.10)
P-value				0.042
Mixed-effects model (intercept only) Change in HbA_{1c} (%) from baseline at 12 months				
Mean (SE)		-0.76 (0.07)	-1.08 (0.19)	-0.22 (0.10)
95% CI		-0.90, -0.62	-1.46, -0.70	-0.43, -0.02
P-value		-	-	0.028
Linear mixed-effects model (FE and RE) Change in HbA_{1c} (%) from baseline at 12 months				
Tx (1=DPP-4 inhibitor; 2=Liraglutide)^				
Coef. (SE)		-	-	-0.19 (0.11)
95% CI		-	-	-0.40, 0.02
p-value		-	-	0.072

CI: confidence interval; Coef: coefficient; FE: fixed effects; HbA_{1c}: haemoglobin A1c; SD: standard deviation; RE: random effects; SE: standard error; TX: treatment.
^Change in HbA_{1c} (coefficient, 95% CI, p-value) adjusted for waist circumference (-0.02, -0.03, 0.01, 0.003) and weight (0.01, 0.00, 0.02, 0.038).

10.4.2 Key secondary effectiveness outcomes

The key secondary effectiveness outcomes were change in SBP (mmHg) and body weight (kg) from baseline at 12 months, which are described in Section 10.4.2.1 and 10.4.2.2 respectively.

10.4.2.1 Change in SBP (mmHg) from baseline at 12 months

Overall 681 subjects (99% out of 688 per-protocol population (pooled data)) had secondary effectiveness data for change in SBP available at baseline and the 12 month time point, which comprised of 346/348 (99.4%) subjects initiated with a DPP-4 inhibitor and 335/340 (98.3%) subjects initiated with liraglutide. There was no significant difference in baseline SBP measurements between the two treatment groups. Based on unadjusted univariate estimates there was a non-statistically significant reduction in SBP of -1.36 mmHg (p=0.261) in those treated with liraglutide compared to DPP-4 inhibitors, Table 10–7.

For the outcome change in SBP at 12 months, following adjustment for patient (fixed) and random effects, the estimated difference between the groups (mean, SE) was -0.64 mmHg (1.28) in favour of liraglutide (p=0.615). This estimate compared to a difference of -1.31 mmHg (1.21) in the

mixed-effects intercept only (p=0.279) and -1.36 mmHg (1.20) in the analysis of the original data (p=0.261).

Table 10–7 Secondary effectiveness variable: Change in SBP (mmHg) from baseline at 12 months

	Overall	DPP-4 inhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide
Per protocol population	**688**	**348**	**340**	
Subjects with data at baseline and 12 months	**681**	**346**	**335**	
SBP measurement at baseline, Mean (SD)	138 (14.7)	137 (14.5)	139 (14.9)	0.223
SBP measurement at 12 months, Mean (SD)	134 (14.7)	134 (15.1)	134 (14.3)	0.932
Change in SBP (mmHg) from baseline at 12 months				
Mean (SD)	-4.40 (13.9)	-3.31 (15.3)	-4.67 (16.1)	-1.36 (1.20)
P-value		-	-	0.261
Mixed-effects model (intercept only) Change in SBP (mmHg) from baseline at 12 months				
Mean (SE) change		-3.10 (1.27)	-4.62 (1.35)	-1.31 (1.21)
95% CI		-5.59, -0.60	-7.27, -1.97	-3.69, 1.06
P-value		-	-	0.279
Linear mixed-effects model (FE and RE) Change in SBP (mmHg) from baseline at 12 months				
Tx (1=DPP-4 inhibitor; 2=Lira.)				
Coef. (SE)		-	-	-0.64 (1.28)
95% CI		-	-	-3.14, 1.86
p-value		-	-	0.615

BMI: body mass index; CI: confidence interval; Coef: coefficient; HbA_{1c}: haemoglobin A1c; FE: fixed effects; SD: standard deviation; RE: random effects; SE: standard error; TX: treatment.
^Change in SBP (coefficient, 95% CI, p-value) adjusted for duration of diabetes (0.01, 0.00, 0.01, 0.010) and BMI (-0.14, -0.22, -0.06, .0.001)

10.4.2.2 Change in bodyweight (kg) from baseline at 12 months

Overall 672 subjects (97.7% out of 688 per-protocol population (pooled data)) had secondary effectiveness data for weight available at baseline and the 12 month time point. This comprised of 341/348 (98%) subjects initiated with DPP-4 inhibitor and 331/340 (97.4%) subjects initiated with liraglutide. The difference in bodyweight was statistically significant between the liraglutide and DPP-4 inhibitor groups at baseline (104kg and 89kg respectively, p<0.001). Based on the

unadjusted univariate estimates there was a significant reduction in bodyweight of -3.12 kg (p<0.001) in those treated with liraglutide compared to DPP-4 inhibitors.

For the outcome change in body weight at 12 months, following adjustment for patient (fixed) and random effects, the estimated difference between the groups (mean, SE) was -2.76 kg (0.54) in favour of liraglutide (p<0.001). This estimate compared to a difference of -1.62 kg (0.40) in the mixed-effects intercept only model (p<0.001) and -2.92 kg in the analysis of the original data (p<0.001), Table 10–8.

Table 10–8 Change in bodyweight (kg) from baseline at 12 months

	Overall	DPP-4 inhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide
Per protocol population (N)	**688**	**348**	**340**	
Subjects with data at baseline and 12 months	**672**	**341**	**331**	
Bodyweight measurement at baseline, Mean (SD)	96.3 (22.2)	89.0 (19.3)	104 (22.5)	<0.001
Bodyweight measurement at 12 months, Mean (SD)	93.2 (21.3)	87.3 (18.6)	99.3 (22.1)	<0.001
Change in body weight (kg) from baseline at 12 months				
Mean (SD)	-3.11 (7.13)	-1.67 (6.45)	-4.59 (7.49)	-2.92 (0.54)
P-value		-	-	<0.001
Mixed-effects model (intercept only) Change in body weight (kg) from baseline at 12 months				
Mean (SE) change		-1.62 9 (0.40)	-4.61 (0.46)	-2.94 (0.50)
95% CI		-2.41, -0.84	-5.51, -3.72	-3.93, -1.95
P-value		-	-	<0.001
Linear mixed-effects model (FE and RE) Change in body weight (kg) from baseline at 12 months				
Tx (1=DPP-4 inhibitor; 2=Lira.)				
Coef. (SE)		-	-	-2.76 (0.54)
95% CI		-	-	-3.83, -1.69
p-value		-	-	<0.001

BMI: body mass index; CI: confidence interval; Coef: coefficient; HbA_{1c}: haemoglobin A1c; FE: fixed effects; SD: standard deviation; RE: random effects; SE: standard error; TX: treatment.
^Change in body weight (coefficient, 95% CI, p-value) adjusted for gender (1.42, 0.23, 2.62, 0.019) waist circumference (0.09, 0.00, 0.17, 0.041), height (-0.06, -0.09, -0.02, 0.002), BMI (-0.23, -0.09, -0.02, 0.006) and HbA_{1c},(0.38, 0.00, 0.77, 0.052).

10.4.3 Other secondary outcomes

10.4.3.1 Other effectiveness outcomes

Data for other effectiveness outcomes included DBP, waist circumference, BMI, and pulse rate. Data at baseline and 12 months are presented in Table 10–9.

Overall 687 subjects (99.9% out of 688 per-protocol population (pooled data)) had secondary effectiveness data for DBP available at the baseline and 12 month time points. This comprised of 348/348 (100%) subjects initiated with a DPP-4 inhibitor and 337/340 (99.1%) subjects initiated with liraglutide. Measures of DBP at baseline and at 12 months were not significantly different between the two treatment groups. The treatment difference for change in DBP from baseline at 12 months between the two treatments was also not statistically significant, 0.02 mmHg (p=0.982).

Overall 147 subjects (21.4% out of 688 per-protocol population (pooled data)) had secondary effectiveness data for waist circumference at baseline and the 12 month time point. This comprised of 92/348 (26.4%) subjects initiated with DPP-4 inhibitor and 93/340 (27.4%) subjects initiated with liraglutide. Measures of waist circumference at baseline and at 12 months were significantly different between those initiated with liraglutide and those initiated with a DPP-4 inhibitor (p<0.001 and p=0.003 respectively). However, the treatment difference for change in waist circumference between the two treatment groups from baseline at 12 months was not statistically significant, 1.99 cm, (p=0.129).

Overall 471 subjects (68.5% out of 688 per-protocol population (pooled data)) had secondary effectiveness data for BMI at baseline and the 12 month time point. This comprised of 249/348 (71.6%) subjects initiated with DPP-4 inhibitor and 222/340 (65.3%) subjects initiated with liraglutide. Measures of BMI at baseline and at 12 months were significantly different between the two treatment groups (p<0.001 and p<0.001 respectively). Based on unadjusted univariate estimates the change in BMI from baseline at 12 months was statistically significant in subjects initiated with liraglutide, -1.51 kg/m^2, compared to those initiated with DPP-4 inhibitors -0.55kg/m^2, (p<0.001).

Overall 347 subjects (50.3% out of 688 per-protocol population (pooled data)) had secondary effectiveness data for pulse rate at baseline and the 12 month time point. This comprised of 176/348 (50.6%) subjects initiated with DPP-4 inhibitor and 171/340 (50.3%) subjects initiated with liraglutide. Measures of DBP at baseline and at 12 months were not significantly different between the two treatment groups. The treatment difference for change in pulse rate from baseline at 12 months was also not statistically significant different between the two treatments, 0.26 bpm (p=0.820).

Table 10–9 Additional effectiveness variables from baseline at 12 months

Clinical measurements	Overall Mean (SD)	DPP-4 inhibitor	Liraglutide Mean (SD)	DPP-4 inhibitor vs.

		Mean (SD)		Liraglutide (P-value)
Per Protocol population (N)	**688**	**348**	**340**	
DBP (mmHg)				
Subjects with data at baseline and 12 months	685	348	337	
DBP (mmHg) measurement at baseline,	79.2 (9.57)	78.6 (9.03)	79.9 (10.1)	0.084
DBP (mmHg) measurement at 12 months	78.4 (10.9)	77.8 (10.7)	79.0 (11.0)	0.123
Change from baseline at 12 months	-0.84 (11.8)	-0.84 (12.0)	-0.82 (11.5)	0.982
Waist circumference (cm)				
Subjects with data at baseline and 12 months	147	72	75	
Waist circumference measurement at baseline	112.1 (15.09)	107.4 (13.81)	116.7 (14.95)	<0.001
Waist circumference measurement at 12 months	110.5 (14.96)	106.8 (14.81)	114.1 (14.31)	0.003
Change from baseline at 12 months	-1.61 (7.92)	-0.60 (10.02)	-2.59 (5.05)	0.129
BMI (kg/m^2)				
Subjects with data at baseline and 12 months	471	249	222	
BMI measurement at baseline	34.2 (6.86)	31.7 (5.87)	36.8 (6.85)	<0.001
BMI measurement at 12 months	33.2 (6.56)	31.2 (5.81)	35.3 (6.60)	<0.001
Change from baseline at 12 months	-1.01 (2.16)	-0.55 (1.64)	-1.51 (2.53)	<0.001
Pulse rate (bpm)				
Subjects with data at baseline and 12 months	347	176	171	
Pulse rate measurement at baseline	75.82 (9.55)	75.48 (9.79)	76.2 (9.32)	0.500
Pulse rate measurement at 12 months	75.57 (12.23)	75.35 (13.6)	75.8 (10.98)	0.739
Change from baseline at 12 months	-0.26 (10.4)	-0.13 (12.4)	-0.39 (7.97)	0.820

BMI: body mass index, DBP: diastolic blood pressure, SBP: systolic blood pressure, SD: standard deviation

10.4.3.2 Measures of resource utilisation

Data was collected for number of GP visits (diabetes-related and total), number of secondary care visits, number of prescribed test strips, per subject at baseline and at the time points 3 (±1), 6 (±1) and 12 (-3/+6, i.e. 9 to 18) months following therapy initiation. Data at baseline and 12 months are presented in Table 10–10 and Table 10–11. Data at time points 3 and 6 months are presented in Appendix, See Annex 1.

Data was also collected for changes in concomitant glucose lowering medications, and changes in anti-hypertensive and cholesterol-lowering medications, per subject, at baseline and 12 (-3/+6, i.e. 9 to 18) months following therapy initiation.

GP visits and secondary care

Overall 584 subjects (84.9% out of 688 per-protocol population (pooled data)) had data for diabetes-related GP visits at baseline. This comprised of 287/348 (82.5%) subjects initiated with a

DPP-4 inhibitor and 297/340 subjects initiated with liraglutide. At the 12 month time point, 592/688 (86%) subjects had data for diabetes-related GP visits, which comprised of 287/348 (82.5%) subjects initiated with a DPP-4 inhibitor and 292/340 (85.9%) initiated with liraglutide.

Overall 587 subjects (85.3% out of 688 per-protocol population (pooled data)) had data for total GP visits at baseline. This comprised of 296/348 (85.1%) subjects initiated with a DPP-4 inhibitor and 291/340 (85.6%) subjects initiated with liraglutide. At the 12 month time point, 596/688 (86.6%) subjects (pooled data) had data for total GP visits, which comprised of 306/348 (87.9%) subjects initiated with a DPP-4 inhibitor and 290/340 (85.3%) initiated with liraglutide.

Overall 412 subjects (59.9% out of 688 per-protocol population (pooled data)) had data for secondary care visits at baseline. This comprised of 201/348 (57.8%) subjects initiated with a DPP-4 inhibitor and 211/340 (62.1%) subjects initiated with liraglutide. At the 12 month time point, 373/688 (54.26%) subjects (pooled data) had data for total GP visits, which comprised of 188/348 (54.0%) subjects initiated with a DPP-4 inhibitor and 185/340 (54.4%) initiated with liraglutide.

At baseline (6 months before therapy initiation), subjects initiated with liraglutide had significantly more diabetes-related (p=0.036) and total (p=0.001) primary and secondary (p=0.014) care visits, as seen in Table 10–10. From baseline at 12 months, only secondary care visits remained significantly different, with 0.98 visits for liraglutide-treated subjects versus 0.62 visits for subjects initiated with DPP-4 inhibitors (p=0.001).

Table 10–10 Primary and secondary care visits at baseline and 12 months, by drug: Pooled data and by treatment

	Pooled	DPP-4 inhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide (p-value)
Per protocol population (N)	**688**	**348**	**340**	
Number of visits at baseline				
Diabetes related GP visits				
Subjects with data	584	287	297	
Visits at baseline Mean, SD	2.44 (1.54)	2.31 (1.42)	1.23 (1.64)	0.036
Total GP visits				
Subjects with data	587	296	291	
Total GP visits Mean, SD	4.11 (30.8)	3.71 (2.66)	4.52 (3.41)	0.001
Secondary care visits				
Subjects with data	412	201	211	
Mean, SD	1.05 (1.56)	0.86 (1.32)	1.23 (1.74)	0.014

	Pooled	DPP-4 inhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide (p-value)
Number of visits at 12 months				
Diabetes related GP visits				
Subjects with data	592	287	292	
Mean, SD	3.17 (2.96)	3.08 (3.31)	3.26 (2.55)	0.466
Total GP visits				
Subjects with data	596	306	290	
Mean, SD	5.42 (4.29)	5.20 (4.34)	5.65 (4.23)	0.201
Secondary care visits				
Subjects with data	373	188	185	
Mean, SD	0.80 (1.07)	0.62 (1.01)	0.98 (1.10)	0.001
Hospitalisation				
Subjects with data	320	162	158	
Mean, SD	0.63 (1.68)	0.58 (1.69)	0.68 (1.67)	0.606
Inpatient visits				
Subjects with data	294	150	144	
Mean, SD	0.94 (4.36)	0.97 (5.02)	0.90 (3.56)	0.900

GP: general practitioner; SD: standard deviation

The relationship between primary and secondary care utilisation and observed covariates was investigated in a linear mixed-effects analysis (see Section 9.9.2.1). In the adjusted models, the allocation to liraglutide or a DPP-4 inhibitor was not a significant predictor of the change in resource utilisation following initiation. The change in resource utilisation was attributable in this analysis to differences in patient characteristics: significant predictors of the change in diabetes related GP visits was duration of diabetes, baseline SBP, baseline BMI, and baseline complications (0=none; 1 otherwise); significant predictors of the change in secondary care visits was age and gender, Table 10–11.

Table 10–11 Linear mixed models (FE and RE): DPP-4 inhibitor vs. liraglutide (resource utilisation)

	Coef	SE	p-value	LL	UL
Change in diabetes related GP visits					

	Coef	SE	p-value	LL	UL
Duration_0	0.00	0.00	0.063	-0.01	0.00
SBP_0	0.01	0.00	0.006	0.00	0.02
BMI_0	-0.02	0.01	0.049	-0.05	0.00
Complications_0	0.54	0.28	0.056	-0.01	1.10
Change in secondary care visits					
Age	-0.01	0.00	0.009	-0.02	0.00
Gender_0	0.30	0.16	0.056	-0.01	0.62

BMI: body mass index, Coef: coefficient, FE: fixed effects, LL: lower limit of 95% confidence interval, RE: random effects, SBP: systolic blood pressure, SE: standard error, UL: upper limit of 95% confidence interval.
Statistical significance has been extended to up to 6.3% for covariates to improve model fit.
_0 indicates baseline.

Self-monitoring blood glucose test strip use

Data was collected for number of prescribed SMBG test strips per-subject at baseline (prescriptions over last 6 months), and at the time points 3 (±1), 6 (±1) and 12 (-3/+6, i.e. 9 to 18) months following therapy initiation. Number of prescribed SMBG test strips per-subject over the time period from baseline to time points 3 (±1), 6 (±1) and 12 (-3/+6, i.e. 9 to 18) months was recorded. Data at 12 months is presented. Data at time points 3 and 6 months are provided in Appendix 4, see Annex 1.

Overall 335 subjects (48.7% out of 688 per-protocol population (pooled data)) had data for prescribed SMBG test strips. This comprised of 169/348 (48.6%) subjects initiated with DPP-4 inhibitor and 166/340 (48.8%) subjects initiated with liraglutide. At the 12 month time point, 379/688 (55.1%) subjects (pooled data) had data for prescribed SMBG test-strips, which comprised of 180/348 (51.7%) subjects initiated with DPP-4 inhibitor and 199/340 (58.5%) initiated with liraglutide.

Test-strip prescriptions were comparable throughout the study period, as seen in Table 10–12.

Table 10–12 Per-subject self-monitoring blood glucose test-strip prescriptions at baseline and 12 months, by drug: Pooled data and by treatment

	Pooled	DPP-4 inhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide (p-value)
Per-protocol population	688	348	340	
Test strip prescriptions at baseline				

	Pooled	DPP-4 inhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide (p-value)
Subjects with data	335	169	166	
Mean, SD	31.7 (64.4)	31.6 (62.3)	31.9 (66.7)	0.970
Test-strip prescriptions at 12 months				
Subjects with data	379	180	199	
Mean, SD	73.5 (157)	72.5 (175)	74.5 (139)	0.900

SD: standard deviation.

Changes in concomitant glucose lowering medications

Data was collected for changes in concomitant glucose lowering medications per subject. Overall 629 subjects (91.4% out of 688 per-protocol population (pooled data)) had concomitant resource utilisation data available at baseline. This comprised of 318/348 (91.4%) subjects initiated with DPP-4 inhibitor and 311/340 (91.5%) subjects initiated with liraglutide. At the 12 month time point 634 subjects (92.2% out of 688 per-protocol population (pooled data)) had concomitant resource utilisation data available, which comprised of 321/348 (92.2%) subjects initiated with DPP-4 inhibitor and 313/340 (92.1%) subjects initiated with liraglutide.

At baseline, the frequency of use of metformin was significantly greater in subjects initiated with liraglutide than subjects initiated with DPP-4 inhibitors, as seen in Table 10–13, and this difference was maintained throughout the 12-month treatment period. Frequency of SU use was also significantly higher at baseline in subjects initiated with liraglutide, but was not statistically different by the end of the 12-month period.

Table 10–13 Number of subjects receiving concomitant blood glucose lowering therapy at baseline, 12 months and change from baseline at 12 months, by drug: pooled data and by treatment group

	Pooled	DPP-4 inhibitor	Liraglutide	DPP-4 inhibiotr vs. Liraglutide (p-value)
Per protocol population (N)	**688**	**348**	**340**	
Subjects with data at baseline	**629**	**318**	**311**	
Subjects with data at 12 months	**634**	**321**	**313**	
Number of subjects receiving concomitant blood glucose lowering therapy at baseline, n (%)				
Met	549 (87.3%)	264 (83.0%)	285 (91.6%)	0.002

	Pooled	DPP-4 inhibitor	Liraglutide	DPP-4 inhibiotr vs. Liraglutide (p-value)
SU	263 (41.8%)	120 (37.7%)	143 (46.0%)	0.044
Pioglitazone	57 (9.06%)	29 (9.12%)	28 (9.00%)	1.000
Acarbose	9 (1.41%)	5 (1.55%)	4 (1.27%)	1.000
Meg	29 (4.61%)	12 (3.77%)	17 (5.47%)	0.411
Number of subjects receiving concomitant blood glucose lowering therapy at 12 months, n (%)				
Met	561 (88.5%)	270 (84.1%)	291 (93.0%)	0.001
SU	280 (44.2%)	131 (40.8%)	149 (47.6%)	0.101
Pioglitazone	62 (9.78%)	32 (9.97%)	30 (9.58%)	0.977
Acarbose	10 (1.56%)	5 (1.54%)	5 (1.58%)	1.000
Meg	32 (5.05%)	14 (4.36%)	18 (5.75%)	0.537
Change number of subjects receiving concomitant blood glucose lowering therapy from baseline to 12 months, n (%)				
Met	12 (1.87%)	6 (1.85%)	6 (1.89%)	
SU	17 (2.65%)	11 (3.38%)	6 (1.89%)	
Pioglitazone	5 (0.78%)	3 (0.92%)	2 (0.63%)	
Acarbose	1 (0.16%)	0 (0.00%)	1 (0.32%)	
Meg	3 (0.47%)	2 (0.62%)	1 (0.32%)	

Met: metformin; SU: sulphonylurea; Meg: meglitinides.

Change in anti-hypertensive and cholesterol-lowering medications

Data was collected for changes in anti-hypertensive and cholesterol-lowering medication per subject at baseline and at the 12 month (-3/+6, i.e. 9 to 18) time point only.

Overall 589 subjects (85.6% out of 688 per-protocol population (pooled data)) had data for anti-hypertensive and cholesterol-lowering medication use at baseline. This comprised of 296/348 (85.1%) subjects initiated with DPP-4 inhibitor and 293/340 (86.2%) subjects initiated with liraglutide. At the 12 month time point, 598 subjects (86.9% out of 688 per-protocol population (pooled data)) had data for anti-hypertensive and cholesterol-lowering medication use, which comprised of 301/348 (86.5%) subjects initiated with DPP-4 inhibitor and 297/340 (87.4%) initiated with liraglutide.

Use of anti-hypertensive and cholesterol-lowering medications was comparable between the treatment groups at baseline, and this was unchanged throughout the study period, as seen in Table 10–14 and Table 10–15. More subjects were taking anti-hypertensive medications than cholesterol-lowering medications.

Table 10–14 Change in use of anti-hypertensive medications over 12 months: Pooled data and by treatment arm

	Pooled	DPP-4 inhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide (p-value)
Per protocol population (N)	**688**	**348**	**340**	
Subjects with data at baseline	**589**	**296**	**293**	
Subjects with data at 12 months	**598**	**301**	**297**	
Number taking anti-hypertensive medication at baseline, (n, %)	509 (86.4%)	254 (85.8%)	255 (87.0%)	0.755
Number taking anti-hypertensive medication at 12 months (n, %)	521 (87.1%)	260 (86.4%)	261 (87.9%)	0.67
Difference from baseline at 12 months (%)	0.7%	0.6%	0.8%	

Table 10–15 Change in use of cholesterol-lowering medications over 12 months: Pooled data and by treatment arm

	Pooled	DPP-4 inhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide (p-value)
Per protocol population (N)	**688**	**348**	**340**	
Subjects with data at baseline	**589**	**296**	**293**	
Subjects with data at 12 months	**598**	**301**	**297**	
Subjects taking cholesterol-lowering medication at baseline (n, %)	419 (71.1%)	214 (72.3%)	205 (70.0%)	0.594
Subjects taking cholesterol-lowering medication at 12 months (n, %)	435 (72.7%)	223 (74.1%)	212 (71.4%)	0.515
Difference from baseline at 12 months (%)	1.6%	1.8%	1.4%	

10.4.3.3 Safety results and diabetes related complications

Safety

Safety information, if reported in patient medical records, was captured in the eCRF. Clinicians were instructed to describe any adverse events, in the course of treatment, that were reported by the patient. There were two fields for data entry "did you report any Adverse Events to the authorities?" and "did the patient report any intolerability?" where the clinician could write a free text response.

Overall, GPs completed the field "did you report any adverse events to the authorities?" for 381 subjects (55.4% out of 688 per-protocol population (pooled data)). GPs reported no AEs to the authorities from baseline at 12 months following treatment initiation for subjects where data were available (381/381).

Overall, GPs completed the field "did the patient report any intolerability?" for 388 subjects (56.4% out of 688 per-protocol population (pooled data)). GPs reported adverse events (AEs) in 12/388 (3.09%) subjects (pooled data), which consisted of 1/203 (0.00%) of subject initiated with DPP-4 inhibitors and 11/185 (5.9%) subjects initiated with liraglutide. These were mainly due to gastrointestinal (GI) AEs known to be associated with liraglutide treatment, Table 10–16. Free-text responses describing GP recorded adverse events in Table 10–16 are listed in Table 10–17.

Table 10–16 Summary of GP recorded adverse events

Adverse event, n (%)	DPP-4 inhibitor	Liraglutide	Overall
Per protocol population	**348**	**340**	**688**
Subjects with data	**203**	**185**	**388**
Reported adverse events, n (%)			
Nausea	0	10 (5.4%)	10 (2.6%)
Vomiting	0	1 (0.01%)	1 (0.00%)
Unknown reason*	1 (0.00%)	0	1 (0.00%)

AE: adverse event
*Unknown reason. GP entered "[redacted]"

Table 10–17 Free-text responses describing GP recorded adverse events by country

Country	DPP-4 inhibitor	Liraglutide (native language)
France	[redacted]	
Germany		

Country	DPP-4 inhibitor	Liraglutide (native language)
Spain	[redacted]	
UK		

*Translated. Native language wording in brackets.

Diabetes related complications

Data was collected for number of diabetes related complications at baseline and at the time points 3 (±1), 6 (±1) and 12 (-3/+6, i.e. 9 to 18) months following therapy initiation. Data at baseline and 12 months is presented Table 10–18. Data at time points 3 and 6 months are provided in Appendix 4, see Annex 1.

At baseline, there was a statistically significant difference in the prevalence of obesity and macroalbuminuria between the two patient groups for pooled data from the four European countries, Table 10–18. At the 12 month assessment period of treatment, only obesity remained significantly different between the two groups; however, the reduction in prevalence of obesity in the liraglutide was numerically greater than in the DPP-4 inhibitor group. There were no hypoglycaemic episodes reported over the 12 months from treatment initiation in those initiated with liraglutide in the study, Table 10–18.

Table 10–18 Change in total diabetes related complications at baseline, 12 months and from baseline at 12 months, by drug: Pooled data and by treatment group

	Pooled	DPP-4vinhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide (p-value)
Per protocol population (N)	**688**	**348**	**340**	
Subjects with data at baseline	**688**	**348**	**340**	
Subjects with data at 12 months	**688**	**348**	**340**	
Complications at baseline, n (%)				
IHD	71 (10.3%)	31 (8.91%)	40 (11.8%)	0.269
MI	17 (2.47%)	10 (2.87%)	7 (2.06%)	0.658
Cerebrovascular disease	30 (4.36%)	13 (3.74%)	17 (5.00%)	0.532
Stroke	15 (2.18%)	10 (2.87%)	5 (1.47%)	0.318

	Pooled	DPP-4vinhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide (p-value)
PVD	41 (5.96%)	22 (6.32%)	19 (5.59%)	0.806
Hypertension	487 (70.8%)	239 (68.7%)	248 (72.9%)	0.252
Hypercholesterolemia	143 (38.9%)	71 (37.8%)	72 (40.0%)	0.739
Obesity	356 (51.7%)	134 (38.5%)	222 (65.3%)	<0.001
Sleep apnoea	30 (4.36%)	11 (3.16%)	19 (5.59%)	0.17
Retinopathy	69 (10.0%)	31 (8.91%)	38 (11.2%)	0.388
Neuropathy	63 (9.16%)	24 (6.90%)	39 (11.5%)	0.051
Nephropathy	48 (6.98%)	25 (7.18%)	23 (6.76%)	0.947
Macroalbuminuria	5 (0.73%)	0 (0.00%)	5 (1.47%)	0.029
Microalbuminuria	67 (9.74%)	33 (9.48%)	34 (10.0%)	0.92
Hypoglycaemia	3 (0.44%)	1 (0.29%)	2 (0.59%)	0.62
Other	14 (3.80%)	7 (3.72%)	7 (3.89%)	1.000
Complications at 12 months, n (%)				
IHD	63 (9.16%)	25 (7.18%)	38 (11.2%)	0.092
MI	18 (2.62%)	9 (2.59%)	9 (2.65%)	1.000
Cerebrovascular disease	22 (3.20%)	10 (2.87%)	12 (3.53%)	0.786
Stroke	14 (2.03%)	11 (3.16%)	3 (0.88%)	0.065
PVD	36 (5.23%)	22 (6.32%)	14 (4.12%)	0.26
Hypertension	422 (61.3%)	206 (59.2%)	216 (63.5%)	0.276
Hypercholesterolemia	124 (33.7%)	64 (34.0%)	60 (33.3%)	0.973
Obesity	312 (45.3%)	118 (33.9%)	194 (57.1%)	<0.001
Sleep apnoea	31 (4.51%)	11 (3.16%)	20 (5.88%)	0.124
Retinopathy	76 (11.0%)	34 (9.77%)	42 (12.4%)	0.338
Neuropathy	47 (6.83%)	18 (5.17%)	29 (8.53%)	0.111
Nephropathy	53 (7.70%)	26 (7.47%)	27 (7.94%)	0.93
Macroalbuminuria	6 (0.87%)	1 (0.29%)	5 (1.47%)	0.119
Microalbuminuria	62 (9.01%)	30 (8.62%)	32 (9.41%)	0.819
Hypoglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.000
Other	12 (3.26%)	7 (3.72%)	5 (2.78%)	0.828

	Pooled	DPP-4vinhibitor	Liraglutide	DPP-4 inhibitor vs. Liraglutide (p-value)
Change in complications from baseline at 12 months, n (%)				
IHD	-8 (-1.16%)	-6 (-1.72%)	-2 (-0.59%)	
MI	1 (0.15%)	-1 (-0.29%)	2 (0.59%)	
Cerebrovascular disease	-8 (-1.16%)	-3 (-0.86%)	-5 (-1.47%)	
Stroke	-1 (-0.15%)	1 (0.29%)	-2 (-0.59%)	
PVD	-5 (-0.73%)	0 (0.00%)	-5 (-1.47%)	
Hypertension	-65 (-9.45%)	-33 (-9.48%)	-32 (-9.41%)	
Hypercholesterolemia	-19 (-2.76%)	-7 (-2.01%)	-12 (-3.53%)	
Obesity	-44 (-6.4%)	-16 (-4.6%)	-28 (-8.24%)	
Sleep apnoea	1 (0.15%)	0 (0.00%)	1 (0.29%)	
Retinopathy	7 (1.02%)	3 (0.86%)	4 (1.18%)	
Neuropathy	-16 (-2.33%)	-6 (-1.72%)	-10 (-2.94%)	
Nephropathy	5 (0.73%)	1 (0.29%)	4 (1.18%)	
Macroalbuminuria	1 (0.15%)	1 (0.29%)	0 (0.00%)	
Microalbuminuria	-5 (-0.73%)	-3 (-0.86%)	-2 (-0.59%)	
Hypoglycaemia	-3 (-0.44%)	-1 (-0.29%)	-2 (-0.59%)	
Other	-2 (-0.29%)	0 (0.00%)	-2 (-0.59%)	

IHD: ischaemic heart disease; MI: myocardial infarction; PVD: peripheral vascular disease.

10.4.3.4 Healthcare professional perceptions of liraglutide and DPP-4 inhibitor therapy and factors determining therapy choice as assessed by Healthcare professionals

The primary HCPs were also asked to identify the most important factor determining therapy choice (liraglutide or DPP-4 inhibitor). Overall, HCPs completed the question for 688/688 subjects.

Table 10–19 presents the frequency of reasons given for drug initiation, averaged across the four European countries. Results indicated that treatment efficacy was the predominant reason for drug initiation in both treatment groups. The top reason for choice of drug initiation was the potential to achieve HbA_{1c} % target, followed by the combination of glucose- and weight-lowering effects in the liraglutide group (21.8% versus 7.2%); and glucose lowering efficacy in the DPP-4 inhibitor group (26.4% versus 15.0%). The mode of administration was not a notable reason for therapy initiation in either DPP-4 inhibitor (4.3%) or liraglutide (0.9%) groups.

Table 10–19 Reason for initiation of therapy as assessed by HCP

	DPP-4 inhibitor	Liraglutide
Per protocol population (N)	**348**	**340**
Subjects with data	**348**	**340**
Reason, n (%)		
1: Mode of administration	15 (4.3%)	3 (0.9%)
2: Patient acceptance/preference	32 (9.2%)	21 (6.2%)
3: Glucose lowering efficacy	92 (26.4%)	51 (15.0%)
4: Potential to achieve HbA_{1c} % target	179 (51.4%)	148 (43.5%)
5: Effects on body weight	5 (1.4%)	43 (12.6%)
6: Combination of glucose and weight lowering effects	25 (7.22%)	74 (21.8%)
7: Cost	0 (0.0%)	0 (0.0%)

$HbA_{1c,}$: haemoglobin A1c

When recording the 12 (-3/+6, i.e. 9 to 18) month observations, data reflecting qualitative endpoints assessing primary HCP perceptions of liraglutide and DPP-4 inhibitor therapy were collected by means of series of questions using a linear 10 point visual analogue scale (VAS) scale (see below). Overall, HCPs completed the question for 688/688 subjects. Three questions (Q1, Q4 and Q5) asked for HCP opinion, and two questions (Q2 and Q3) asked how HCPs perceived subject opinion, Table 10–20.Questions asked were:

Q1: For you as a GP, how difficult was it to initiate and maintain this patient on drug X?
10 extremely easy – 0 extremely difficult
Q2: For the patient, how big of an issue is the mode of administration?
10 No concern – 0 Extremely concerned
Q3: How satisfied is the patient with drug X?
10 Extremely satisfied – 0 Extremely dissatisfied
Q4: How satisfied have you been with drug X in this patient?
10 Extremely satisfied – 0 Extremely dissatisfied
Q5: How cost-effective do you think drug X has been for this patient?
10 Extremely cost effective – 0 No health economic value

Although healthcare professionals scored DPP-4 inhibitors more favourably than liraglutide therapy, both therapies scored favourably across all questions. HCP's found it Easy to initiate subjects onto either DPP-4 inhibitors or liraglutide.

HCPs did not perceive mode of administration to be a problem for subjects, although as expected liraglutide scored lower than DPP-4 inhibitors, which is likely due the need to inject liraglutide and not DPP-4 inhibitors.

HCPs scored both DPP-4 inhibitors and liraglutide favourably for HCP satisfaction with therapy, patient satisfaction, HCP perceived cost effectiveness.

Table 10–20 Healthcare professional perceptions of liraglutide and DPP-4 inhibitor therapies using a visual analogue scale

	Q1 Initiate and maintain n (%)	Q2 mode of administration n (%)	Q3 Patient satisfaction n (%)	Q4 HCP satisfaction n (%)	Q5 Cost-effectiveness n (%)
DPP-4 inhibitor (N=348)					
10	136 (39.1%)	172 (49.4%)	75 (21.6%)	65 (18.7%)	32 (9.20%)
9	95 (27.3%)	65 (18.7%)	70 (20.1%)	67 (19.3%)	71 (20.4%)
8	57 (16.4%)	55 (15.8%)	98 (28.2%)	78 (22.4%)	70 (20.1%)
7	30 (8.62%)	26 (7.47%)	56 (16.1%)	53 (15.2%)	64 (18.4%)
6	9 (2.59%)	4 (1.15%)	13 (3.74%)	27 (7.76%)	31 (8.91%)
5	14 (4.02%)	16 (4.60%)	25 (7.18%)	34 (9.77%)	49 (14.1%)
4	5 (1.44%)	4 (1.15%)	5 (1.44%)	12 (3.45%)	12 (3.45%)
3	1 (0.29%)	0 (0.00%)	4 (1.15%)	6 (1.72%)	12 (3.45%)
2	1 (0.29%)	5 (1.44%)	1 (0.29%)	4 (1.15%)	5 (1.44%)
1	0 (0.00%)	1 (0.29%)	1 (0.29%)	2 (0.57%)	2 (0.57%)
Liraglutide (N=340)					
10	77 (22.6%)	65 (19.1%)	65 (19.1%)	63 (18.5%)	30 (8.82%)
9	56 (16.5%)	53 (15.6%)	39 (11.5%)	42 (12.4%)	42 (12.4%)
8	69 (20.3%)	64 (18.8%)	90 (26.5%)	84 (24.7%)	66 (19.4%)
7	61 (17.9%)	71 (20.9%)	56 (16.5%)	50 (14.7%)	60 (17.6%)
6	26 (7.65%)	45 (13.2%)	31 (9.12%)	21 (6.18%)	27 (7.94%)
5	41 (12.1%)	30 (8.82%)	38 (11.2%)	38 (11.2%)	50 (14.7%)
4	4 (1.18%)	7 (2.06%)	12 (3.53%)	23 (6.76%)	21 (6.18%)
3	3 (0.88%)	4 (1.18%)	5 (1.47%)	14 (4.12%)	31 (9.12%)
2	2 (0.59%)	0 (0.00%)	2 (0.59%)	3 (0.88%)	6 (1.76%)
1	1 (0.29%)	1 (0.29%)	2 (0.59%)	2 (0.59%)	7 (2.06%)
DPP-4 inhibitor vs. Liraglutide					
P-value	<0.001	<0.001	0.002	0.142	0.01

Questions included:
Q1: For you as a GP, how difficult was it to initiate and maintain this patient on drug X?
10 extremely easy – 0 extremely difficult
Q2: For the patient, how big of an issue is the mode of administration?

	Q1 Initiate and maintain n (%)	Q2 mode of administration n (%)	Q3 Patient satisfaction n (%)	Q4 HCP satisfaction n (%)	Q5 Cost-effectiveness n (%)
10 No concern – 0 Extremely concerned					
Q3: How satisfied is the patient with drug X?					
10 Extremely satisfied – 0 Extremely dissatisfied					
Q4: How satisfied have you been with drug X in this patient?					
10 Extremely satisfied – 0 Extremely dissatisfied					
Q5: How cost-effective do you think drug X has been for this patient?					
10 Extremely cost effective – 0 No health economic value					

Table 10–21 reports the outcomes for subjects initiated with either liraglutide or a DPP-4 inhibitor stratified by the clinician's reported reason for therapy choice. Clinicians were asked to specify the reason for treatment allocation of patients to each group (liraglutide or DPP-4 inhibitor) based on the following factors: mode of administration, patient acceptance/preference, glucose lowering efficacy, potential to achieve HBA_{1c} target, effects on bodyweight or combination of glucose and weight lowering effects. The liraglutide group was associated with statistically significant reductions in HbA_{1c} (-0.98 vs -0.77, difference -0.21, p=0.041) and weight (-4.59 vs -1.67, difference -2.92, p<0.001), and an absolute reduction in SBP (-4.67 vs -3.31, difference -1.36 p>0.05).

Liraglutide was associated with significantly greater reductions in HbA_{1c} of -0.36 (p<0.1) and -1.06 (p<0.05) for individuals initiated with liraglutide for the reason of 'glucose lowering efficacy' or the 'combination of 'glucose and weight lowering effects'. Liraglutide was associated with an absolute greater reduction in weight across clinicians reported reasons for treatment initiation.

Table 10–21 Change in key primary and secondary clinical outcomes from baseline at 12 months by treatment reason

		1: Mode of administration	2: Patient acceptance/preference	3: Glucose lowering efficacy	4: Potential to achieve HbA1c % target	5: Effects on body weight	6: Combination of glucose and weight lowering effects	Total
DPP-4 inhibitor	N	15	32	92	179	5	25	348
	HbA_{1c} (%)	-0.65	-0.80	-0.82	-0.85	0.49	-0.22	-0.77
	Weight (Kg)	-1.23	-1.10	-1.07	-1.87	0.10	-3.69	-1.67
	SBP (mmHg)	-9.87	1.28	-3.14	-4.22	4.80	-1.00	-3.31

		1: Mode of administration	2: Patient acceptance/preference	3: Glucose lowering efficacy	4: Potential to achieve HbA1c % target	5: Effects on body weight	6: Combination of glucose and weight lowering effects	Total
Liraglutide	N	3	21	51	148	43	74	340
	HbA_{1c} (%)	-0.33	-0.58	-1.18	-0.91	-0.69	-1.29	-0.98
	Weight (Kg)	-3.62	-4.36	-3.92	-4.78	-4.89	-4.58	-4.59
	SBP (mmHg)	-3.00	-3.19	-5.60	-3.85	-6.93	-4.91	-4.67
Total	N	18	53	143	327	48	99	688
	HbA_{1c} (%)	-0.59	-0.71	-0.95	-0.88	-0.56	-1.02	-0.87
	Weight (Kg)	-1.63	-2.39	-2.08	-3.19	-4.36	-4.35	-3.11
	SBP (mmHg)	-8.72	-0.49	-3.98	-4.05	-5.68	-3.92	-3.98
Liraglutide vs. DPP-4 inhibitor	HbA_{1c} (%)	0.31	0.22	***-0.36***	-0.06	-1.17	**-1.06**	-0.21
	Weight (Kg)	-2.38	**-3.27**	**-2.85**	**-2.91**	-4.99	-0.89	-2.92
	SBP (mmHg)	6.87	-4.47	-2.45	0.37	-11.73	-3.91	-1.36

SBP: systolic blood pressure, HbA_{1c}: haemoglobin A1c.
* Bold indicates statistically significant at 5% level; bold and italic 10% level

10.4.4 Summary of main results

10.4.4.1 Baseline characteristics

At baseline, patients initiated with liraglutide had significantly greater HbA_{1c}, waist circumference, BMI and weight versus those initiated with a DPP-4 inhibitor (Table 10–1 and Table 10–2). The proportion of subjects being obese was 65.3% at baseline for those initiated with liraglutide and at months 12 the proportion was 57.1% Table 10–18. For those initiated with DPP-4 inhibitors the figures were 38.5% at baseline and 33.9% at 12 months. The proportion of patients being obese reduced numerically more in the liraglutide group.

10.4.4.2 Summary of treatment effectiveness

Although HbA_{1c}, waist circumference, BMI and weight remained statistically different over 12 months of treatment between groups, subjects initiated with liraglutide achieved greater reductions in these variables during therapy, and this was statistically significant for HbA_{1c} and weight (Table 10–6 and Table 10–8). Multivariate statistical analysis adjusting for patient (fixed effects) and country/centre (random effects) confirmed that liraglutide had a greater reduction in HbA_{1c} and body weight compared to the DPP-4 inhibitor group (see Summary Table 10–22).

Table 10–22 Summary of change in main effectiveness outcomes liraglutide versus DPP-4 inhibitor from baseline at 12 months treatment effectiveness estimates

Liraglutide versus DPP-4 inhibitor	Observed (non-imputed) data		Mixed-effects model (intercept only)		Linear mixed models (FE and RE)	
	Mean	p-value	Mean	p-value	Mean	p-value
Change in HbA_{1c} (%)	-0.21	0.042	-0.22	0.028	-0.19	0.072
Change in body weight (kg)	-2.92	<0.001	-2.94	<0.001	-2.76	<0.001
Change in SBP (mmHg)	-1.36	0.261	-1.31	0.279	-0.64	0.615

HbA_{1c}: haemoglobin A1c; FE: fixed effects; SBP: Systolic blood pressure; RE: Random effects; SBP: systolic blood pressure.

10.4.4.3 Summary of resource utilisation

Subjects initiated with liraglutide had significantly more primary and secondary care visits at baseline, but by the end of the study period, primary care visits were similar between the two treatment groups, Table 10–10. Speculatively, higher secondary care utilisation in the liraglutide group may be attributable to higher rates of diabetes-related complications (i.e. event-related admissions) in subjects initiating therapy with liraglutide compared to the DPP-4 inhibitor group at baseline and at 12 months. For instance, at baseline the subjects in the liraglutide group had a higher incidence of obesity, neuropathy, and macroalbuminuria, Table 10–18. Multivariate statistical analysis adjusting for patient (fixed effects) and country/centre (random effects) suggested that complications at baseline was a significant predictor of GP visits; however, study drug (liraglutide or DPP-4 inhibitor) was not a significant predictors of resource utilisation, with differences in resource utilisation between the study groups attributed to differences in patient characteristics, Table 10–19.

Subjects initiated with liraglutide were also more likely to be receiving concomitant metformin and SUs at baseline; while the change in metformin use was comparable between the treatment groups, fewer subjects initiated concomitant SU use during the study period, Table 10–14. Differences in dose of oral glucose lowering agents could not be evaluated from the data, which was inconsistently captured, and where dose was recorded, differences in product descriptions and units thwarted a valid assessment.

10.4.4.4 Perceptions

Healthcare professionals acknowledged the benefits of liraglutide therapy during questionnaires. The main factors driving the choice of liraglutide therapy were "the potential to achieve the HbA_{1c} target" and the "glucose- and/or weight-lowering effects", Table 10–19. Although DPP-4 inhibitors were scored more favourably for ease of administration, this was rarely stated as the main factor influencing therapy choice, indicating that the injectable administration of liraglutide therapy was not a barrier to liraglutide therapy. For subjects initiating liraglutide for its 'glucose lowering efficacy' or the 'combination of 'glucose and weight lowering effects' properties, significantly greater reductions in HbA_{1c} of -0.36 ($p<0.1$) and -1.06 ($p<0.05$) were observed (no control for multiple comparisons). Further, significantly greater reductions in body weight for liraglutide subjects were observed for those initiating liraglutide for the reasons of 'patient acceptance or preference', 'glucose lowering efficacy' and 'potential to achieve HbA_{1c} target'

10.5 Other analyses

10.5.1 Pooled data at 3 and 6 month time points

Pooled data at 3 and 6 month time points are provided in Appendix 4, see Annex 1

10.5.2 Analysis by country

Analysis by country is provided in Appendix 5, see Annex 1.

10.5.3 Sensitivity analysis

Analysis of the entire patient cohort (N=952) excluding the approach to correct timeframe for observations (see Section 9.8.5) are provided in Appendix 6, see Annex 1

10.5.4 Cost-effectiveness analysis

Cost-effectiveness analysis is provided in Appendix 7, see Annex 1.

10.6 Adverse events and/or adverse reactions

As the study was retrospective in nature involving anonymised electronic health care records it was not feasible to make a causality assessment at the individual case level. Please see Section 10.4.3.3 for safety results.

10.6.1 Adverse events

11/185 (5.9%) subjects initiated with liraglutide experienced gastrointestinal AEs related to nausea or vomiting. Please see Section 10.4.3.3 for safety results. Overall no new safety events were identified as part of this study.

10.6.2 Deaths, other serious adverse events and other significant adverse events

10.6.2.1 Deaths

Inclusion criteria required subjects to have measurements at baseline and 12 months (-3 +6 i.e. 9 to 18 months), for inclusion in the study. Study design therefore meant deaths were not recorded.

10.6.2.2 Other serious adverse events

Due to study design, and the extent of data collection, the severity of reported adverse events could not be determined.

10.6.2.3 Other significant adverse events

No other significant adverse events were reported.

10.6.3 Other observations related to safety

Other observations related to safety included the prevalence of diabetes related complications, including hypoglycaemia, which are described earlier in Section 10.4.3.3.

10.6.4 Summary of adverse events

Only gastrointestinal adverse events (5.9% in subjects initiated with liraglutide) were captured in this study. Gastrointestinal adverse events are an identified risk and are the most frequently reported adverse events in subjects treated with liraglutide (frequency in clinical trials: 1,207 per 1,000 patient-years of exposure (PYE)).[1] To improve gastrointestinal tolerability when initiating liraglutide treatment, dose escalation is recommended in the product information.[1] There were no other observations related to safety reported during the study. Overall, this observational study did not identify any new safety concerns; the benefit risk profile continues unaltered.

11 Discussion

11.1 Key results

Study NN2211-4077 was a retrospective, primary care-based case study with the primary objective of exploring the clinical effectiveness, safety and place in clinical practice of liraglutide and DPP-4 inhibitor therapy in routine primary care across four European countries: France, Germany, Spain and the UK.

Baseline demographics were generally comparable across countries, but there were some significant differences between subjects initiated with liraglutide and subjects initiated with DPP-4 inhibitors for certain demographics. Prescribing decisions may reflect clinicians' perception of the suitability of a treatment (e.g. its therapeutic profile) to a patient's characteristics. Data here showed there is a male predominance for those initiated with liraglutide in the UK (63.9%), compared to a female predominance in Spain (67.6%). Duration of diabetes prior to therapy initiation was longer for subjects in the UK 120 months [10 years] in DPP-4 inhibitor initiates, and 160 months [13.3 years] liraglutide initiates), and shorter in Germany 78.6 months [6.6 years] in DPP-4 inhibitor initiates, and 78.9 months [6.6 years] liraglutide initiates) compared to the pooled dataset.

The primary variable in determining clinical effectiveness was glycaemic control (assessed as change in HbA_{1c}), while weight and SBP formed key secondary effectiveness variables. Other variables that were also recorded included WC, DBP, BMI and pulse rate. Baseline clinical measures were also significantly different between those initiated with liraglutide (N=340) and those initiated with a DPP-4 inhibitor (N=348), which may have affected results. Mean HbA_{1c}, BMI and weight at baseline were all significantly higher in subjects initiated with liraglutide compared to those initiated with a DPP-4 inhibitor. Differences in these variables remained statistically different over 12 months of treatment, subjects initiated with liraglutide achieved greater reductions during therapy, and this was statistically significant for HbA_{1c}, and weight

Multivariate analyses, which adjusted for recorded differences between subjects in each group in terms of clinical and demographic profiles, country and centre effects, were also undertaken. These analyses estimated that subjects initiated with liraglutide had a statistically significant greater reduction in HbA_{1c} compared to those initiated with a DPP-4 inhibitor, which was consistent with estimates from the actual (non-imputed) data; however lower baseline HbA1c in the liraglutide vs DPP-4 inhibitor group may have contributed to this finding. Nonetheless, the multivariate analyses add strength to the conclusion that liraglutide was associated with greater reductions in HbA_{1c} compared to DPP-4 inhibitors when used in routine clinical practice.

Multivariate analysis was also undertaken for the key secondary variables of weight and SBP. These analyses estimated that subjects initiated with liraglutide achieved a significant reduction in body weight, compared to those initiated with a DPP-4 inhibitor; while analysis of SBP suggested

that there was no statistically significant difference between groups, with or without adjustment for patient and random effects. However, there was an absolute (numerical) greater reduction in SBP for subjects initiating liraglutide.

The safety of liraglutide in the primary care setting was explored by asking HCPs to record patient experience of adverse events, as well as diabetes-related complications, which included the recording of hypoglycaemia. In total 11/185 (5.9%) of subjects initiated with liraglutide experienced gastrointestinal related AEs. Of these, 5/11 events were described as transient in nature e.g. "[redacted] nausea". There were no other observations related to safety or recorded hypoglycaemia events reported during the study for those initiated with liraglutide. However, due to study design underreporting of safety events would be expected.

The secondary outcomes of the study were to assess the direct resource utilisation of liraglutide and DPP-4 inhibitor therapy in primary care; illustrate the health economic value of liraglutide compared with DPP-4 inhibitor therapy in routine primary care; assess HCPs perception of the utility of liraglutide in relation to DPP-4 inhibitor therapy in routine primary care; assess impact of mode of administration on therapy initiation in routine primary care; and evaluate perceived patient acceptability of liraglutide in relation to DPP-4 inhibitor therapy in routine primary care. In terms of resource use, subjects initiated with liraglutide had significantly more primary and secondary care visits at baseline, but by the end of the study period at 12 months, primary care visits were similar between the treatment groups. Higher secondary care utilisation in the liraglutide group may be attributable to higher rates of diabetes related complications seen in those subjects chosen to initiate liraglutide therapy compared to those subjects chosen to initiate therapy with a DPP-4 inhibitor at baseline and over 12 months. For instance, at baseline the liraglutide group had a higher incidence of obesity, neuropathy and macroalbuminuria. However further evidence would be required to determine any an association. At 12 months, the liraglutide group had a higher incidence of obesity, as well as IHD ($p<0.1$). Conversely, the DPP-4 inhibitor group had a higher incidence of stroke at 12 months ($p<0.1$). Multivariate (adjusted) analyses suggest treatment drug (liraglutide or a DPP-4 inhibitor) were not related to changes in resource utilisation following initiation; rather patient characteristics, including the presence of diabetes related complications at baseline for primary care visits, were significant factors in explaining the observed change in resource use over 12 months.

Subjects initiated with liraglutide were also more likely to be receiving concomitant metformin and SUs at baseline; however there was no significant difference between the groups in terms of SU usage at 12 months. Similarly, the change in metformin usage over 12 months was comparable between the treatment groups, although there was a minor increase in SU and metformin use at 12 months in both groups, which may be expected as treatment intensification may follow the natural progression of T2DM over time. In this study the reported oral glucose lowering product types and units (dose) was inconsistent and incomplete and is therefore a potential limitation of this analysis; the quantity and strength of concomitant oral agents used by subjects may be a significant

confounder in observed patient outcomes. However, the number of concomitant oral agents at baseline and the change in the number of concomitant oral agents at 12 months were evaluated in multivariate (adjusted) analyses and were not found to be significant predictors of the primary and key secondary clinical effectiveness measures (HbA_{1c}, body weight and SBP).

Healthcare professionals acknowledged the benefits of liraglutide therapy by questionnaires. The top reason for choice of drug initiation with liraglutide was the potential to achieve HbA_{1c} % target, followed by the combination of glucose- and weight-lowering effects in the liraglutide group (21.8% versus 7.2%); and glucose lowering efficacy in the DPP-4 inhibitor group (26.4% versus 15.0%). Although DPP-4 inhibitors were scored higher for ease of administration, this was rarely stated as the main factor influencing therapy choice. The treatment satisfaction data reflected HCP opinion. Overall HCPs scored both DPP-4 inhibitors and liraglutide favourably for both patient satisfaction, HCP satisfaction, and HCP perceived cost effectiveness.

11.2 Limitations

There are a number of potential limitations associated with the accurate collection of data from the participating centres. Missing and erroneous data was present in the data collected from sites; these issues were documented and addressed in the pre-analysis phase of the study (data cleaning) and adjusted for use in the final analysis by use of statistical techniques (multiple imputation). Nonetheless, there may remain sources of bias in the data associated with clinicians completing report forms accurately and hence with the accuracy of data entry. The questionnaire used was a non-validated prior to its application; however clinical response to survey questions was reasonable.

The types of subjects initiated with liraglutide or a DPP-4 inhibitor appeared to be two distinct patient populations with statistically different baseline characteristics. This could have been influenced by the HCPs perceptions regarding the suitability of patients to the drug profiles of either liraglutide or DPP-4 inhibitors. Subjects initiated with liraglutide had higher $HbA_{1c,}$ were obese, had a longer duration of diabetes, higher prevalence of diabetes related complications (obesity, neuropathy and macroalbuminuria) were more likely to be receiving concomitant metformin and SUs and had significantly more primary and secondary care visits at baseline. However, subjects initiated with liraglutide achieved a greater reduction in outcomes relevant to diabetes therapy, when compared to baseline values, including HbA_{1c}. This difference in patient phenotype limits the validity of comparison between the groups and reducing the extent to which comparative conclusions can be drawn.

Due to difficulties in recruiting the initially planned number subjects in the primary care settings in France and Spain (France: 94, Spain: 67), data collection was stopped early in these countries. Consequently the study was underpowered in order to determine statistical significance in effectiveness outcomes. However, a statistically significant difference between those initiated with liraglutide and DPP-4 inhibitors was detected in unadjusted univariate estimates for HbA_{1c} and

weight, and confirmed for weight in multivariate analysis adjusting for statistically significant covariates.

11.3 Interpretation

The subjects initiated with liraglutide and DPP-4 inhibitors appeared to be two distinct patient populations with statistically different baseline characteristics. This difference in patient phenotype limits the validity of comparison between the groups and reduces the extent to which comparative conclusions can be drawn. However, subjects initiated with liraglutide achieved a greater reduction in outcomes relevant to diabetes therapy, when compared to baseline values, including HbA_{1c} and weight.

Both liraglutide and DPP-4 inhibitor therapy appeared to be well tolerated. There were no deaths, SAEs or discontinuations due to adverse events reported by HCP's for both drugs. Gastrointestinal AEs were reported in 11/185 (5.9%) subjects initiated on liraglutide. Of these, 10/185 (5.4%) were related to nausea, which was often described as transient in nature and was in line with expected adverse events; where transient nausea is listed as a very common AE, affecting 1 in 10[1].

11.4 Generalisability

Recruitment in France and Spain was stopped early due to poor recruitment at the study sites; this limited the sample size and may affect the generalisability of results in these two countries.

The inclusion criteria were broad to enhance the generalisability of study findings. Inclusion criteria were subjects with type 2 diabetes treated with liraglutide or DPP-4 inhibitors, according to license in respective participating country, with data available for 12 (-3/+6, i.e. 9 to 18) months. Subjects were excluded if they had a prior treatment history that included DPP-4 inhibitors or liraglutide, or if they received liraglutide or DPP-4 inhibitor outside of their licensed indications.

The broad inclusion criteria led to variety of subjects recruited into the study, which resulted in different demographic and baseline characteristics between the liraglutide and DPP-4 inhibitor initiates. While this enhanced the generalisability of study findings, this also impacts on the validity of study results as subjects initiated with liraglutide and DPP-4 inhibitors appeared to be two distinct patient populations.

The primary reason for therapy initiation was the ability to achieve HbA_{1c} target. HCP's did not perceive mode of administration to be a barrier to initiating subjects with liraglutide in the primary care setting, and HCP perceptions of subject option where that subjects were not overly concerned with mode of administration.

12 Other information

Additional information is provided as appendices. Please refer to Annex 1 for details.

13 Conclusion

The primary objective of this study was to demonstrate the clinical effectiveness, safety and place in clinical practice of liraglutide and DPP-4 inhibitor therapy in routine primary care across four European countries.

The types of patients initiated with liraglutide or a DPP-4 inhibitor appear to be different, limiting the validity of comparison between the groups and reducing the extent to which comparative conclusions can be drawn. Analyses demonstrated that subjects typically escalated to liraglutide therapy had less well-controlled diabetes and were more often obese. However, subjects initiated with liraglutide achieved a greater reduction in outcomes relevant to diabetes therapy, when compared to baseline values, including body weight and HbA_{1c}.

Liraglutide has demonstrated a clinically relevant effect on glycaemic control in type 2 diabetes patients when administered in the primary care setting. Only gastrointestinal adverse events were captured in this study. Gastrointestinal adverse events are an identified risk and are the most frequently reported adverse events in subjects treated with liraglutide (frequency in clinical trials: 1,207 per 1,000 PYE).[1] With continued therapy, the frequency and severity decreased in most patients who initially experienced nausea. To improve gastrointestinal tolerability when initiating liraglutide treatment, dose escalation is recommended in the product information.[1] Overall, this observational study did not identify any new safety concerns; the benefit risk profile continues unaltered.

Compared to intra-group change from baseline those initiated with DPP-4 inhibitors, this real-world study demonstrated that liraglutide conferred additional health benefits to subjects (greater reduction in HbA_{1c} and body weight), and acceptable, and may be considered an effective treatment option for subjects with uncontrolled T2DM on oral therapy.

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