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EMA/857940/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Victoza

liraglutide

Procedure No.: EMEA/H/C/001026/II/0005/G

Note

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

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
AUC_{0-24h}	area under the plasma concentration – time plot between 0 – 24 hours
$AUC_{GIR\ 0-24h}$	area under the glucose infusion rate curve between 0 and 24 hours after dosing
BMI	body mass index
C_{max}	maximal plasma concentration
C^{ss}_{max}	maximal plasma concentration at steady state
C^{ss}_{min}	minimal plasma concentration at steady state
C^{ss}_{av}	average plasma concentration at steady state
CI	confidence interval
detemir+lira group	metformin + liraglutide 1.8 mg/day + insulin detemir group in Study 1842
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FPG	fasting plasma glucose
GIR	glucose infusion rate
GIR_{max}	maximum glucose infusion rate
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated haemoglobin
lira-control group	randomised metformin + liraglutide 1.8 mg/day group in Study 1842
LOCF	Last Observation Carried Forward
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MESI	medical event of special interest
N	number of subjects
OAD	oral antidiabetic drug
PD	pharmacodynamic
PK	pharmacokinetic
QRD	Quality Review of Documents
RMP	Risk Management Plan
s.c.	subcutaneously
SBP	Systolic blood pressure
SD	standard deviation
SMPG	self-measured plasma glucose
SU	Sulphonyl urea derivate
t_{GIRmax}	time to maximum glucose infusion rate
t_{max}	time to maximum plasma concentration
TEAE	treatment-emergent Adverse Event
T2DM	type 2 diabetes mellitus
TZD	thiazolidinedione
U	Units
UNR	upper normal range
vs.	versus

1. Scientific discussion

1.1. Introduction

About the product

Victoza (liraglutide) is a once-daily human glucagon-like peptide-1 (GLP-1) analogue. Compared to human GLP-1, liraglutide has a C16 fatty (palmitic) acid chain attached at position 26 (lysine) of the peptide, and has a lysine at position 34 replaced by an arginine. When administered subcutaneously (s.c.), these structural modifications result in PK properties of the compound suitable for once daily administration. Mode of action trials in subjects with type 2 diabetes mellitus (T2DM) have demonstrated glucose lowering, increased insulin secretion, restored beta-cell responsiveness to increasing glucose concentrations and delayed gastric emptying after a single s.c. dose of liraglutide.

Victoza is administered as a once-daily s.c. injection, irrespective of meals, in either the upper arm, thigh or abdomen at therapeutic doses of 1.2 mg or 1.8 mg. The product is available in a 3 mL prefilled pen.

Victoza was approved throughout the European Union on 30 June 2009.

Victoza is indicated in adults who have type 2 diabetes to control their blood glucose level. Victoza is used together with:

- metformin or a sulphonylurea (anti-diabetes medicines) in patients whose glucose levels are not satisfactorily controlled on metformin or a sulphonylurea used on their own at the maximum possible dose

- metformin and a sulphonylurea, or metformin and a thiazolidinedione in patients whose glucose levels are not satisfactorily controlled despite treatment with two medicines.

Problem statement

The MAH submitted a grouping of two type II variations. The first variation application was an extension of the indication for Victoza for the treatment of type 2 diabetes mellitus in combination with basal insulin in patients not achieving adequate glycaemic control with Victoza and metformin alone. The second variation was submitted by the MAH to include a warning in the Victoza SmPC that Victoza is not a substitute for insulin following spontaneous reported cases of ketoacidosis in patients switching from insulin to Victoza.

The variations submitted in the group are the following:

Variation(s) requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The scopes applied for by the MAH were as follows:

- Extension of indication for the treatment of type 2 diabetes in combination with basal insulin in patients not achieving adequate glycaemic control with Victoza and metformin alone: update to sections 4.1, 4.5, 4.8 and 5.1 of the SmPC and consequential changes to sections 1 and 2 of the Package Leaflet.
- Update to section 4.4 of the SmPC to include a warning that Victoza is not a substitute for insulin and consequential changes to section 2 of the Package Leaflet, following post-marketing spontaneous reports of ketoacidosis in patients switching from insulin to Victoza. In addition the MAH has taken the opportunity to align the Annexes with version 7.3.1 of the QRD template and to delete the DDPS version number from Annex IIB. Minor editorial changes have been made throughout the Annexes. Finally in section 6 of the Package Leaflet, the pictures for the instructions of using Victoza have been changed so that the fingers in the pictures are now white instead of yellow.

Overall introduction

Two new clinical studies have been submitted by the MAH with this grouping of two type 2 variations:

- Clinical pharmacology trial NN2211-3673, to provide information on PK and PD of the basal insulin and liraglutide combination in patients with T2DM.

- Clinical study NN2211-1842, performed in T2DM patients to investigate the efficacy and safety of adding basal insulin detemir to the combination therapy of liraglutide and metformin when these agents no longer provide adequate glycaemic control.

Trials and Data Included in the Clinical Overview

Confirmatory Phase 3b Efficacy and Safety Trial	**Supportive Phase 1 Pharmacokinetics and Pharmacodynamics Trial**
Trial NN2211-1842 in insulin-naïve subjects with type 2 diabetes: After a 12-week run-in period with metformin and liraglutide, two regimens were compared: 1: liraglutide 1.8 mg + metformin 2: insulin detemir + liraglutide 1.8 mg + metformin	Trial NN2211-3673 in subjects with type 2 diabetes Treatments: • liraglutide steady-state dose of 1.8 mg • insulin detemir 0.5 U/kg • liraglutide 1.8 mg + insulin detemir 0.5 U/kg

In order to demonstrate the contribution of Victoza in the efficacy of the combination metformin + basal insulin + liraglutide therapy, the MAH identified comparable patient populations to provide data on the efficacy and the safety of the basal insulin and metformin combination. The following three sources were used:

- Literature search

- An International Variability Evaluation (PREDICTIVE) search (PREDICTIVE™ is a global observational study including 30 countries following type 1 and type 2 patients initiated on Levemir. The primary objective of the study is to document the safety using Levemir)

- All available Levemir clinical trials were used to identify patients with comparable patient populations.

GCP

Both the clinical pharmacology and the confirmatory clinical trial were conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice, as declared by the MAH.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/288/2010) for the following condition(s):

- Type 2 diabetes mellitus

on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

1.2. Clinical aspects

1.2.1. Clinical Pharmacology

Study NN2211-3673

This clinical pharmacology study was an open-label phase I study conducted in 33 male or female, insulin-naïve subjects with type 2 diabetes. This study was designed to investigate whether the PK and PD properties of insulin detemir and/or liraglutide would be affected when the two drugs were co-administered to subjects with type 2 diabetes. The objective of the trial was to compare the 24-hour concentration profile – the area under the concentration–time curve (AUC0–24h) – and the maximum serum concentration (C_{max}) after administration of insulin detemir administered alone and when co-administered with liraglutide at a steady-state dose of 1.8 mg/day.

Overview of Clinical Pharmacology, Trial 3673

Country	N Race/Ethnicity	Trial Design	Doses (Daily)
US	33 (23M/10F) 26 Caucasian 6 Afro-American 1 Asian	Open-label, A: single-dose insulin detemir (PK & euglycaemic clamp), B: steady-state liraglutide (PK & euglycaemic clamp) C: steady-state liraglutide + single-dose detemir (PK & euglycaemic clamp)	insulin detemir: 0.5 U/kg liraglutide: Escalating from 0.6, 1.2 and 1.8 mg ending with a steady-state dose of 1.8 mg

Abbreviations: M/F = males to females; N = number of subjects; PK = pharmacokinetic; U = unit.

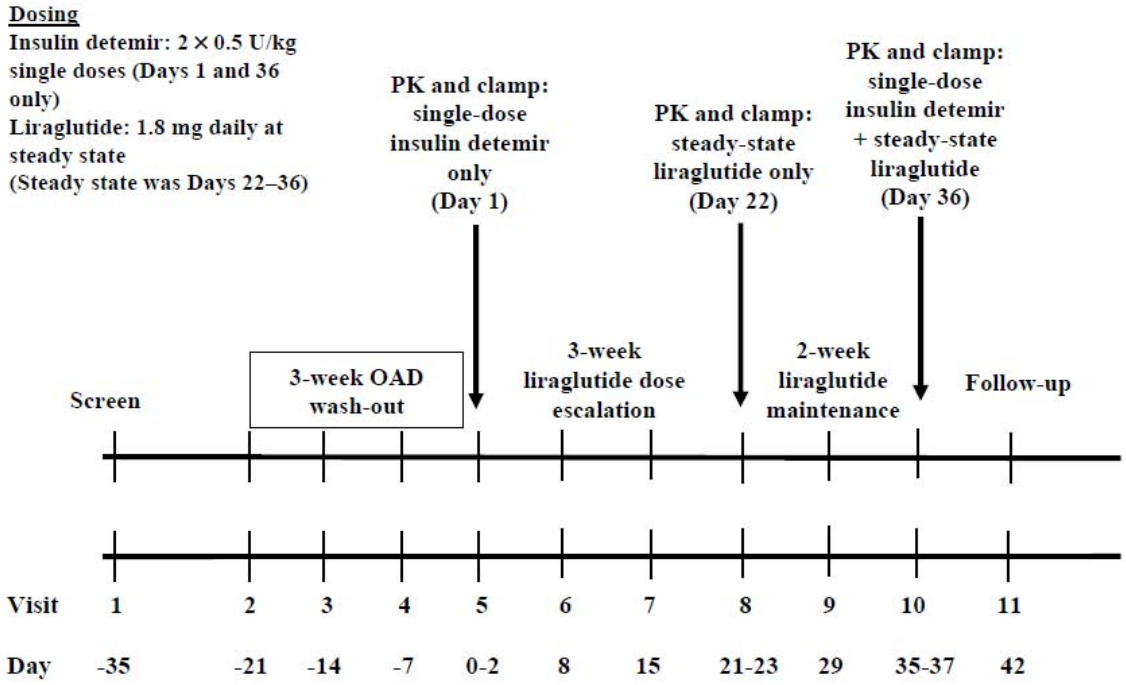
Methods

Study NN2211-3673 was an open label phase I trial including a total of 33 men and women aged 18 years or more with type 2 diabetes.

Study participants

According to the inclusion criteria the subjects were required to be insulin naïve subjects diagnosed with type 2 diabetes and treated with stable doses of OADs (one of which had to be metformin), body mass index (BMI) of ≤45 kg/m2, screening glycosylated haemoglobin (HbA1c) of 7-10% on monotherapy and 7-9.5% on dual therapy, Fasting Plasma Glucose (FPG) ≤250 mg/dL at Visit 2, FPG ≥140 and ≤240 mg/dL at Visit 5.

Study design (study NN2211-3673)



Following successful screening (Visit 1), subjects entered a 3-week washout period and discontinued oral anti-diabetic drugs (OADs), other than metformin (subjects on metformin monotherapy preceded to the Visit 5 clamp). During the washout, weekly telephone contact visits and the glucose diary were reviewed. After the washout period (Visit 5-Day 1) all subjects had a 24 hr euglycaemic clamp (100 mg/dL) following dosing with 0.5 U/kg insulin detemir and 24 hour serial insulin detemir PK was assessed. Following the detemir clamp, all subjects began a liraglutide titration (0.6 mg/day on days 2-8, 1.2 mg/day on days 9-15 and 1.8 mg/day on days 16-22). On Day 22, a 24 hour liraglutide PK profile and euglycaemic clamp (following 1.8 mg liraglutide) was performed in all subjects. Subjects were then maintained on liraglutide 1.8 mg/day for another 14 days with a telephone contact visit/diary review on Day 29. At Visit 10 (Day 36), subjects had a third euglycaemic clamp following co-administration of liraglutide (1.8 mg) and insulin detemir (0.5 U/kg). The liraglutide and insulin detemir PK profile was assessed. A final visit was scheduled at Day 42 ± 3 days (Visit 11).

PK and PD properties were investigated in three euclycaemic clamp settings scheduled 2-3 weeks apart during an 11-week study period with metformin as the only background treatment.

For the assessment of the PK profile of Liraglutide plasma samples were collected at 0 min (pre-dose) and 2, 4, 6, 8, 9, 10, 11, 12, 14, 16, 18 and 24 hours post liraglutide dose.

For the assessment of the PK profile of insulin detemir samples (serum) were collected at 0 min (pre-dose) and 2, 4, 6, 8, 9, 10, 11, 12, 14, 16, 18 and 24 hours post insulin detemir dose. The insulin detemir and liraglutide concentrations were determined with validated ELISA methods.

Information on the pharmacodynamic effects of the study medication was derived from the glucose infusion rate (GIR). The clamp started with a run in period of 2 hours before start of medication, insulin was used in order to maintain blood glucose levels of 5.5 mmol/L (100 mg/dL). Basal insulin infusion was discontinued approximately 30 minutes prior to dosing. After administration of the study medication (insulin detemir, liraglutide or both) glucose infusion was used in order to obtain a blood glucose level of 5.5 mmol/L (100 mg/dL) ± 10%. GIR was recorded. The clamp procedure was continued until blood glucose values reached > 6.6 mmol/L (120 mg/dL) for at least two hours without glucose infusion. The C_{max} of study drug should be achieved before glucose infusion can be stopped. When the clamp was discontinued prior to 24 hours, blood glucose concentrations were monitored for the remaining 24-hour post-dose period.

Treatments

The treatments used in this study included insulin detemir (0.5 U/kg) and liraglutide 1.8mg. A single dose of insulin detemir was given at Visit 5, Day 1 and Visit 10, Day 36. Liraglutide was self-titrated to 1.8mg from Day 2 to Day 22 upon which it was administered at steady state for clamp procedural activity. Subjects then maintained the liraglutide 1.8mg dose for two weeks after which liraglutide and insulin detemir were co-administered for the final clamp procedure on Day 36.

Subjects were directed to administer insulin detemir in the abdomen and liraglutide consistently in one location throughout the trial (either in the abdomen, thigh or upper arm) once daily by subcutaneous injections with the pen-injector. Metformin was considered a background treatment and was regarded as a non-investigational product.

Analytical methods

The analytical reports and method validation reports of the determination for liraglutide in plasma and the determination of insulin detemir were submitted. The insulin detemir concentrations were determined with an enzyme-linked immunosorbent assay (ELISA) method. The liraglutide concentrations were determined with an enzyme-linked immunosorbent assay (ELISA) method.

Outcome/endpoints

- Efficacy

Primary endpoint was the ratio of insulin detemir AUC_{0-24h} and C_{max} (from liraglutide and insulin detemir co-administration clamp divided by insulin detemir alone clamp).

The secondary endpoints included:

- tmax for insulin detemir
- Liraglutide steady state AUC0-24h, Css_{max}, Css_{min}, Css_{av} and t_{max}
- Clamp $AUCGIR_{0-24h}$, $tGIR_{max}$ and GIR_{max} for three clamps

- AUC, C_{max} and C_{min} for plasma insulin, C-peptide and glucagon concentrations (insulin detemir, liraglutide and liraglutide co-administered with insulin detemir)

▪ Safety

Safety was evaluated by monitoring of treatment-emergent adverse events, incidence of hypoglycaemic episodes, physical examination, vital signs, ECG, medical events of special interest and clinical laboratory tests (including liraglutide antibodies).

Statistical Methods

▪ Efficacy

The summary statistics and statistical analyses for the primary and secondary endpoints were based on the Full Analysis Set (FAS). The FAS was defined as all treated subjects exposed to at least one dose of the trial product.

To compare insulin detemir (Levemir) AUC_{0-24h} and C_{max} (with vs. without liraglutide co-administration) the ratio of the AUC_{0-24h} and C_{max} of both treatments were compared using a linear mixed effect model. Treatment (with or without liraglutide) was included as fixed factor and subject as a random factor. From this model, the geometric mean treatment ratio was estimated, and a 90% confidence interval for this was calculated. If the 90% confidence interval lies entirely within the no effect boundary interval 0.80-1.25, it was concluded that there is no PK interaction.

To compare liraglutide steady state PK parameters AUC_{0-24h} and Css_{max} (with vs. without insulin detemir co administration), the analysis was performed in the same manner as for the primary endpoints.

To compare clamp parameters GIR_{max} and $AUCGIR_{0-24h}$ between insulin detemir and insulin detemir with co administration of liraglutide, the clamp parameters GIR_{max} and $AUCGIR_{0-24h}$ were (after log-transformation) analysed separately using a linear mixed effect model with treatment (insulin detemir alone, liraglutide alone, and insulin detemir with co-administration of liraglutide) as fixed factor and subject as a random factor. Pair wise comparisons were made between insulin detemir and insulin detemir with co-administration of liraglutide and between liraglutide and liraglutide with co-administration of insulin detemir.

▪ Safety

Safety endpoints included biochemistry, haematology with differential, urinalysis, physical examinations, vital signs, ECG, FPG and adverse event monitoring. Summary statistics for FPG in raw scale and change from baseline at each scheduled visit were provided. Hypoglycaemic episodes were classified according to ADA definition. Hypoglycaemic episodes were summarised on ADA definition and minor hypoglycaemic episodes definition.

Results

Participant flow

A total of 33 male and female subjects (≥18 years of age) were randomised and enrolled in the study, 32 subjects completed the study. One subject withdrew consent on Visit 5, Day 1 after receiving a dose of insulin detemir and partially completing the clamp procedure. This subject was included in the full analysis set (used for safety analyses), but not the PK or PD analysis set.

Baseline data

The demography of the trial population is presented below.

Table 1: Demography of Trial Population

	Mono* at Screening	Dual** at Screening	Total
Number of Subjects	20	13	33
Age (yrs) Mean (SD) 49.64 (8.47) Min ; Max	 49.60 (9.16) 33.0 ; 68.0	 49.69 (7.65) 36.0 ; 61.0	 33.0 ; 68.0
Sex (n (%)) Male Female	 12 (60.0) 8 (40.0)	 11 (84.6) 2 (15.4)	 23 (69.7) 10 (30.3)
Race (n (%)) White Black Or African American Asian	 16 (80.0) 3 (15.0) 1 (5.0)	 10 (76.9) 3 (23.1) 0	 26 (78.8) 6 (18.2) 1 (3.0)
Ethnicity (n (%)) Hispanic Or Latino Not Hispanic Or Latino	 12 (60.0) 8 (40.0)	 5 (38.5) 8 (61.5)	 17 (51.5) 16 (48.5)
Weight (kg) Mean (SD) Min ; Max	 93.67 (22.12) 59.4 ; 137.9	 105.09 (20.57) 81.8 ; 143.6	 98.17 (21.94) 59.4 ; 143.6
Height (cm) Mean (SD) Min ; Max	 167.98 (9.07) 147.0 ; 183.5	 177.00 (7.97) 158.5 ; 189.0	 171.53 (9.63) 147.0 ; 189.0
BMI (kg/m^2) Mean (SD) Min ; Max	 33.05 (6.68) 23.1 ; 44.0	 33.55 (6.17) 26.8 ; 43.4	 33.25 (6.39) 23.1 ; 44.0
HbA1c (%) Mean (SD) Min ; Max	 8.32 (0.98) 7.0 ; 10.0	 8.25 (0.83) 7.0 ; 9.3	 8.29 (0.91) 7.0 ; 10.0
FPG (mg/dL) Mean (SD) Min ; Max	 175.3 (32.36) 141 ; 230	 172.1 (23.54) 142 ; 217	 174.0 (28.84) 141 ; 230

No Subjects withdrew during washout.
** Subjects on Metformin monotherapy at screening.*
*** Subjects on dual therapy (Metformin + other OAD) at screening.*
Baseline is at visit 5 for weight, BMI and FPG. HbA1c is measured at visit 1.

Outcomes and estimations

- Efficacy

The results of the PK/PD study are presented below.

Table 2: Pharmacokinetic parameters for Insulin Detemir (non-transformed values; arithmetic mean ± SD, t_{max} median, range) N=32

Treatment	**AUC_{0-24h}** pmol/Ll/h	**C_{max}** pmol/L	**t_{max}** h
Detemir	51878 ± 11807	3729 ±912	9.50 (6.0-18.0)
Detemir + Liraglutide	53774 ± 13940	3963 ± 1119	9.50 (4.0-18.0)
LSmean Ratio (90% CI)	1.03 [0.97, 1.09]	1.05 [0.98, 1.13]	-

Table 3: Pharmacokinetic parameters for Liraglutide (arithmetic mean ± SD, t_{max} median, range) N=32

Treatment	AUC_{0-24h} pmol/Ll/h	C_{max} pmol/L	C_{min} pmol/L	C_{av} h	t_{max} h
Liraglutide	328167 ± 93263	17639 ± 5155	8501 ± 3701	13674 ± 3886	11.00 (4.0 - 18.1)
Detemir + Liraglutide	319835 ± 107679	18189 ±6162	8461 ±3825	13327 ±4487	10.00 (4.0 - 18.0)
LSmean Ratio (90% CI)	0.97 [0.87, 1.08]	1.03 [0.93, 1.13]	1.02 [0.87, 1.20]	0.97 [0.87, 1.08]	-

The 90% CIs of ratios of AUC_{0-24h} and C_{max} of insulin detemir and of AUC_{0-24h}, C^{ss}_{max}, C^{ss}_{min}, C^{ss}_{av} for liraglutide steady state were are all within the *no effect* boundary of [0.80, 1.25].

Co-administration of liraglutide with insulin detemir did not greatly affect the t_{max} of either drug.

Table 4: Pharmacodynamic parameters of GIR (arithmetic mean ± SD, t_{GIRmax} median, range N=32

Treatment	$AUC_{GIR0-24h}$ mg/kg	GIR_{max} mg/(kg*min)	t_{GIRmax} hr	SGIRmax mg/(kg*min)	tSGIRmax hr
Detemir	1058 ± 803	13.38 ± 5.85	13.26 (0.75 - 22.58)	2.16 ± 1.03	12.28 (4.32 - 23.50)
Liraglutide	1982 ± 1168	10.13 ± 6.31	9.85 (0.22 - 22.73)	3.01 ±1.25	12.18 (3.50 - 24.00)
Detemir + Liraglutide	2947 ± 1461	11.76 ± 4.38	11.87 (0.00 - 18.02)	3.87 ±1.68	12.84 (0.00 ; 24.00)

Table 5: The Least Square Means Estimate (Ratio) of the different treatments

	Detemir+ Liraglutide/ Detemir*	Detemir+ Liraglutide/ Liraglutide**	Liraglutide/Detemir***
AUC(GIR(0-24h))(mg/kg) Ratio Estimate 95% CI P-value	 2.98 [1.84 , 4.81] .0000	 1.32 [0.82 , 2.14] .2516	 2.25 [1.39 , 3.64] .0013
SGIRmax (mg/(kg*min)) Ratio Estimate 95% CI P-value	 1.78 [1.34 , 2.36] .0001	 1.18 [0.89 , 1.57] .2360	 1.50 [1.13 , 1.99] .0055

The sum of the mean AUC_{GIR} for liraglutide (1982 mg/kg) and insulin detemir (1058 mg/kg) given individually was similar to that obtained when the two were given in combination (2947 mg/kg).

C-peptide average (AVG_{0-24hr}) and maximum concentration (C_{max}) was greatest when liraglutide was administered alone (950.3 pmol/L and 1348.0 pmol/L, respectively).

The plasma insulin data was inconclusive as the assay did not discriminate between endogenous insulin and insulin detemir

Glucagon average (AVG_{0-24hr}) and C_{max} were greatest when insulin detemir was given alone (65.1 pg/mL and 92.1 pg/mL, respectively).

- Safety

A total of 32 subjects experienced a total of 107 adverse events over the duration of the trial. On clamp procedure days, 14 (42.4%) subjects treated with insulin detemir, 17 (51.5%) subjects treated with liraglutide, and 13 (39.4%) subjects treated with both insulin detemir and liraglutide had treatment emergent adverse events. Out of these 32 subjects, 15 (45.5%) subjects experiencing a total of 24adverse events which were potentially treatment related, with the majority of subjects (39.4%) having adverse events following liraglutide administration during the liraglutide dose escalation period. The majority of adverse events were judged as 'unlikely' to be related to treatment.

The most frequently occurring TEAEs (occurring in >10% of subjects) were abdominal discomfort, diarrhoea, nausea, weight decrease, and headache. In four subjects decreased weight was reported and 4 injection site reactions were reported during the study period. No adverse events led to study discontinuation. All adverse events were mild to moderate. No severe AEs were reported. No serious adverse events or deaths were reported. Three asymptomatic hypoglycaemic episodes in 2 subjects were reported.

1.2.2. Discussion on Clinical Pharmacology

The design of the study was considered suitable by the CHMP to assess the influence of liraglutide on the PK profile of insulin detemir and vice versa. The term "basal insulin" as proposed by the MAH in section 4.1 of the SmPC was considered too broad by the CHMP as other long-acting insulins have different PK profile compared to insulin detemir. The MAH was requested to amend "basal insulin" by "insulin detemir" as only clinical pharmacology data on the combination liraglutide-insulin detemir has been provided with this application.

Information derived from the glucose infusion rate (GIR) is an acceptable method to study pharmacodynamic interaction. The inclusion criteria for this study have been properly motivated by the MAH. The withdrawal of one study subject was sufficiently justified according to the CHMP. The analytical methods presented by the MAH were considered acceptable and properly validated. The primary and secondary endpoints and the statistical methods were considered acceptable for this type of study. No pharmacokinetic interaction was observed during this PK/PD study. According to the predefined no effect boundary of [0.8, 1.25], liraglutide at steady state did not affect the pharmacokinetic endpoints (AUC, Cmax) of insulin detemir and vice versa. No pharmacokinetic interaction was observed in this study. The study treatments had an additive pharmacodynamic effect. Both treatments and the combination of the treatments were well tolerated.

1.2.3. Clinical efficacy

Study NN2211-1842

Study NN2211-1842, performed in T2DM patients, to investigate the efficacy and safety of adding insulin detemir to the combination therapy liraglutide 1.8 mg+metformin, was submitted by the MAH to support this extension of indication. The purpose of the trial was to determine whether the effect of insulin detemir in combination with liraglutide 1.8 mg and metformin was superior to that of liraglutide 1.8 mg and metformin alone.

Methods

Study NN2211-1842 was a 26 week randomised, open label, parallel group multicentre, multinational trial, that investigated the effect of insulin detemir in combination with liraglutide and metformin

compared to liraglutide and metformin in subjects with T2DM. The trial included a 26 week extension period; total duration of the trial was 52 weeks.

Study participants

The study was performed in 202 centers in the following countries: United States (57), Germany (37), United Kingdom (32), France (19), Italy (18), The Netherlands (16), Spain (14), Canada (7), and Belgium (2).

Main inclusion criteria:

- Subjects diagnosed with type 2 diabetes, insulin naïve and treated with metformin as monotherapy for ≥3 months prior to screening, at a stable dose of ≥1500 mg/day or metformin (≥1500 mg/day) and a sulphonylurea (less than or equal to ½ of the maximum approved dose according to local label), both at a stable dose for ≥3 months prior to screening. Previous short term insulin treatment in connection with inter-current illness was allowed, at the discretion of the investigator
- HbA1c 7.0-10.0% (both inclusive) for subjects on metformin monotherapy, HbA1c 7.0-8.5% (both inclusive) for subjects on metformin in combination with a sulphonylurea
- Age 18-80 years, both inclusive (or as allowed according to local guidelines)

Inclusion criteria at randomisation:

- HbA1c measured at the randomisation visit (Visit 4a) greater than or equal to 7.0%

Main exclusion criteria included previous treatment with insulin and glucose-lowering agents other than those stated in the inclusion criteria, impaired liver and renal function, history of pancreatitis, cancer and known history of unstable angina, acute coronary event, other significant cardiac event.

The patients included in the trial were type 2 diabetic patients insufficiently controlled on metformin treatment and therefore in need of intensification of treatment. This approach is considered appropriate; metformin is the recommended 1st line therapy according to current treatment guidelines (EASD/ADA). It is noticed however, that patients insufficiently controlled on metformin AND SU were also included. This latter sub-population represents a switch design rather than an add-on design. Since SU treated subjects were only allowed to be on a dosage corresponding to less than or equal to ½ of the maximum approved dose this may be acceptable.

Patients with ischaemic heart disease, heart failure NYHA class IV, impaired hepatic function and impaired kidney function were excluded from the trial.

Treatments

Insulin-naïve type 2 diabetic subjects, aged 18-80, treated with metformin monotherapy (≥1500 mg/day for ≥3 months) and HbA1c between 7.0-10.0% (both inclusive); or metformin (≥1500 mg/day) in combination with a sulphonylurea (less than or equal to ½ of the maximum approved dose) resulting in an HbA1c between 7.0-8.5% (both inclusive) underwent screening, and if eligible, entered the 12 week run-in period. During this run-in period, sulphonylurea (SU) treatment was discontinued, while treatment with metformin remained unchanged (same dose and dosing regimen). Treatment with liraglutide was initiated in all patients in 0.6 mg/day weekly increments to allow a final dose of 1.8 mg/day.

Subjects with an HbA1c ≥ 7.0% after the 12-week run-in period were randomised 1:1 to intensification of treatment with open-label insulin detemir (starting dose of 10 U) added to the combination of liraglutide (1.8 mg/day) and metformin (≥1500mg/day), or to continue with liraglutide (1.8 mg/day) and metformin (≥1500mg/day) treatment as control group (see Figure 1). The metformin + liraglutide

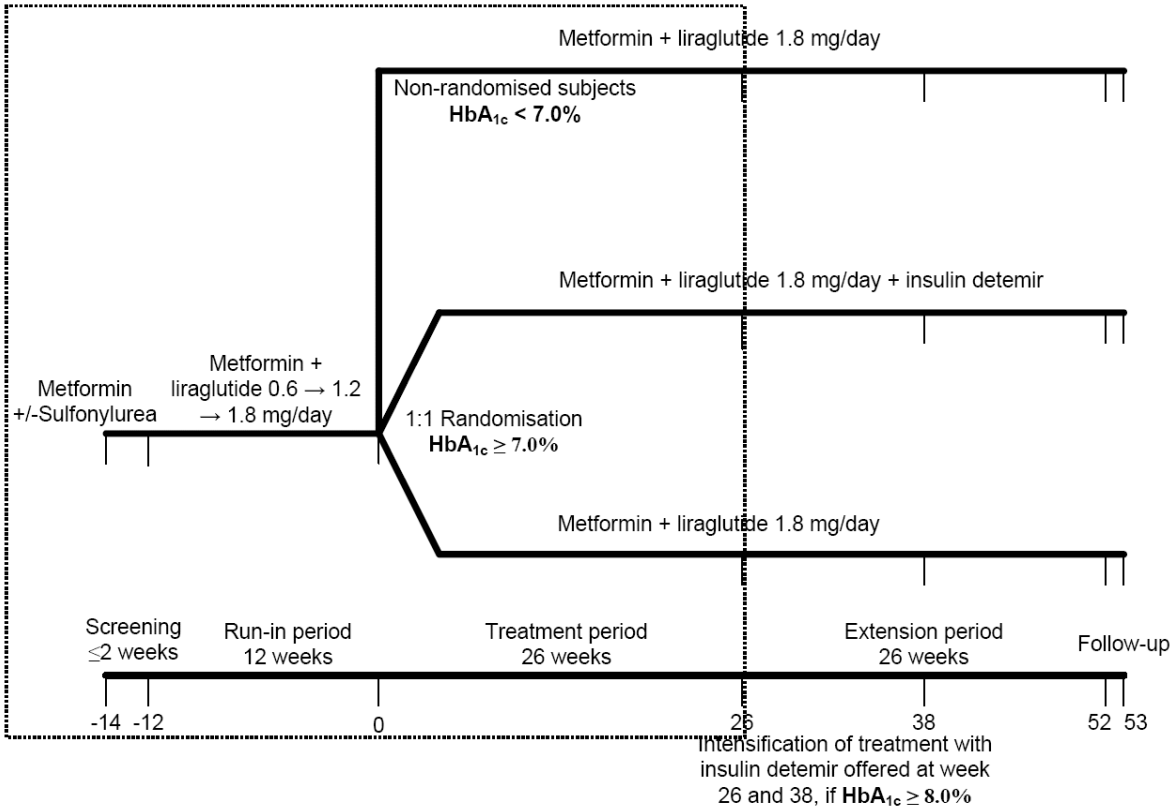
1.8 mg/day + insulin detemir group is referred to as the "detemir+lira group", while the randomised metformin + liraglutide 1.8 mg/day group is referred to as the "lira-control group". The randomisation of subjects to treatment groups was stratified by previous treatment with metformin or a combination of metformin and a SU.

Subjects with an adequate response to liraglutide, i.e. with an HbA1c less than 7.0% after the run-in period, were not randomised, but continued the metformin and liraglutide treatment as in the run-in period.

After the initial dose titration period, liraglutide was to be administered at a constant dose of 1.8 mg throughout the entire trial period. Insulin detemir was initiated at a dose of 10 U per day, with further titration depending on subjects' self-measured glucose values.

After the main 26 week study, subjects could participate in the 26 week extension study. Intensification of treatment with insulin detemir was allowed for subjects both in the randomised and non-randomised liraglutide 1.8 mg + metformin treatment groups with an HbA1c ≥8.0% at week 26 and week 38.

Figure 1: Trial design



----- denotes period included in this clinical trial report.

Objectives

The primary objective was to assess and compare the efficacy (as assessed by HbA1c) of insulin detemir in combination with liraglutide and metformin versus liraglutide and metformin in subjects with type 2 diabetes after 26 weeks of randomized treatment

The secondary objectives were to assess and compare the effects of insulin detemir in combination with liraglutide and metformin versus liraglutide and metformin on other descriptors of glycaemic control (FPG, 7-point self-monitored glucose profiles, proportion of subjects reaching target HbA1c), C-peptide, proinsulin to C-peptide ratio, body weight, waist and hip circumference including the waist to hip ratio, lipids and blood pressure after 26 weeks treatment.

Safety objectives

To assess and compare clinical and laboratory safety parameters and incidence of hypoglycaemic episodes after 26 weeks of treatment.

Outcomes/endpoints

Primary endpoint:

- Change in HbA1c (%) from baseline (randomisation and Week 0) to Week 26.

Secondary endpoints:

- Change in HbA1c from baseline to Week 52 for the two randomised treatment arms using LOCF (applicable for 26-week extension report only)

- Proportion of subjects reaching HbA1c targets at Week 26 (and Week 52 in 26-week extension); American Diabetes Association (ADA) target <7%; American Association of Clinical Endocrinologists (AACE) target ≤6.5%
- Change in glycaemic control parameters from baseline to Week 26 (and Week 52 in extension): Fasting plasma glucose (FPG); Self-measured 7-point (meal-related) glucose profiles, taken before and 90 minutes after the start of breakfast, lunch and dinner, and at bedtime
- Change in body weight from baseline to Week 26 (and Week 52 in 26-week extension)
- Change in waist and hip circumference including waist to hip ratio from baseline to Week 26 (and Week 52 in 26-week extension)
- Change in beta-cell function from baseline to Week 26 (and Week 52 of 26-week extension): Fasting insulin; Fasting pro-insulin; Fasting C-peptide; Pro-insulin to C-peptide ratio; HOMA-B; HOMA-IR
- Change in lipid profile (cholesterol, LDL-C, VLDL-C, HDL-C, triglycerides and FFA) from baseline to Week 26 (and Week 52 in 26-week extension)
- Change in blood pressure (diastolic and systolic) from baseline to Week 26 (and Week 52 in 26-week extension)

Sample size

The trial was powered to demonstrate superiority (delta of 0.5% with a two-sided significance level of 5% and power set to 90%) of insulin detemir + liraglutide 1.8 mg + metformin randomised treatment over liraglutide 1.8 mg + metformin randomised treatment with respect to change in HbA1c from baseline (i.e. randomisation) to Week 26.

The variation in HbA1c was based on the liraglutide phase 3 trials, i.e. a standard deviation (SD) of approximately 1.2%. When using a 1:1 randomisation, the number of subjects required was 123 per group.

The sample size calculations were based on the aim to show superiority of metformin + liraglutide 1.8mg+insulin detemir vs. metformin + liraglutide 1.8mg for the primary endpoint change in HbA1c (delta of 0.5%, a power of 90% and a standard deviation of 1.2%). The calculations also take into account a high drop-out rate in the run-in- as well as during the first 12 weeks of the treatment period. These criteria and assumptions are in line with previous large diabetes trials and are considered acceptable. The high drop-out rates in trials including this patient population are acknowledged.

Randomisation

Patients were randomised 1:1 to receive Insulin detemir + liraglutide 1.8 mg + metformin ≥1500 mg/day or liraglutide 1.8 mg + metformin ≥1500 mg/day

The randomisation of subjects to treatment groups was stratified by previous treatment with metformin or a combination of metformin and a sulphonylurea.

Blinding (masking)

This was an open-labeled trial design.

Statistical methods

The full analysis set (FAS) was used for analyses of all efficacy endpoints and included all randomised subjects who had been exposed to at least one dose of trial products and who provided post-baseline HbA1c efficacy data.

The non-randomised analysis set included all subjects with an HbA1c <7.0% after 12 weeks of run-in and with at least one efficacy value after the randomisation visit. Only descriptive statistics were provided for this group of subjects.

The safety analysis set included all exposed subjects. If a subject received a different treatment than he/she was randomised to, data for the subject was analysed, tabulated and/or listed according to the actual treatment received. All safety evaluations were based on the safety analysis set.

Primary endpoint:

The primary endpoint was analysed using the full analysis set and an analysis of covariance (ANCOVA) of change in HbA1c from baseline to Week 26 for the randomised treatment groups. Treatment, previous OAD and country were explanatory variables and baseline HbA1c values were included as covariates. Missing observations were considered missing at random in all analyses.

Missing values at post baseline visits were replaced using last observation carried forward (LOCF) for analysis purposes.

Secondary endpoints:

FPG, 7-point SMPG profiles, body weight, hip and waist circumference, β-cell function, lipids and blood pressure were all analysed similar to the primary endpoint, i.e. by ANCOVA of change from baseline to week 26 for the randomised treatment groups with treatment, previous OAD and country as explanatory variables, and baseline value as covariate. Proportion of subjects reaching target HbA1c < 7%, or ≦6.5%; after 26 weeks of treatment was analysed using a logistic regression with treatment, previous OAD and country as fixed effect and baseline HbA1c value as covariate.

The secondary endpoints were supportive evidence to the primary endpoint and all tests were two-sided on a significance level of 5%, i.e. no adjustment for multiplicity was applied

▪*Results*

Participant flow

A total of 1658 subjects were screened for this trial (see Table 6). Of these, 670 subjects were screening failures, where the majority (72.2%) failed to meet the HbA1c inclusion criterion. The second most common reason for screening failure was 'other', at 7.8%, with most being withdrawal of consent.

Table 6: Subject disposition

	Lira 1.8 N (%)	Detemir + Lira 1.8 N (%)	Non-randomised Lira 1.8 N (%)	Early WD Lira 1.8 N (%)	All N (%)
Screened					1658
Screening failures					670
Run-in	161	162	498	167	988
Exposed to Liraglutide	161 (100)	162 (100)	498 (100)	166 (100)	987 (100)
Randomised	161 (100)	162 (100)	0 (0.0)	0 (0.0)	323 (32.7)
Main *	161 (100)	162 (100)	498 (100)	0 (0.0)	821 (83.2)
Exposed to Detemir	0 (0.0)	162 (100)	0 (0.0)	0 (0.0)	162 (16.4)
Withdrawals	34 (21.1)	18 (11.1)	28 (5.6)	167 (101)	247 (25.0)
Adverse Events	6 (3.7)	4 (2.5)	9 (1.8)	92 (55.4)	111 (11.2)
Non-compliance with protocol	3 (1.9)	2 (1.2)	7 (1.4)	14 (8.4)	26 (2.6)
Withdrawal criteria	11 (6.8)	0 (0.0)	3 (0.6)	10 (6.0)	24 (2.4)
Protocol deviations	1 (0.6)	3 (1.9)	0 (0.0)	10 (6.0)	14 (1.4)
Lost to follow up	1 (0.6)	1 (0.6)	2 (0.4)	11 (6.6)	15 (1.5)
Ineffective therapy	5 (3.1)	2 (1.2)	0 (0.0)	6 (3.6)	13 (1.3)
Other	7 (4.3)	6 (3.7)	7 (1.4)	24 (14.5)	44 (4.5)
Completers	127 (78.9)	144 (88.9)	470 (94.4)	0 (0.0)	741 (75.1)
Full analysis set	157 (97.5)	162 (100)	0 (0.0)	0 (0.0)	319 (32.3)
Safety analysis set	159 (98.8)	163 (101)	499 (100)	166 (100)	987 (100)

All subjects also received metmin
Early WD: Withdrawals before randomisation visit (visit 4b)
The Full analysis set is based on the treatment the subjects were randomised to.
The Safety analysis set is based on the actual treatment the subjects received.
* 39.3% of subjects entering main period were randomised and 60.7% were non-randomised

A total of 988 subjects entered the run-in phase of the trial and all but one of these subjects were exposed to liraglutide 1.8 mg+metformin. One subject withdrew before being exposed to randomised trial products. About 17% (167 of 988) of subjects withdrew early ('early withdrawals'), i.e. during the run-in period and before randomisation. The most frequent reasons for withdrawal among these subjects were adverse events (mainly gastrointestinal adverse events). Protocol deviations and non-compliance were also common withdrawal reasons in this group, including subjects discovered to violate in- and exclusion criteria after trial start.

A total of 60.7% of the subjects (N=498) completing the run-in phase with liraglutide 1.8 mg+metformin, achieved adequate glycaemic control and continued the trial in the nonrandomised treatment arm. The remaining 39.3% of subjects who did not achieve adequate glycaemic control with an HbA1c below 7% after completing the run-in phase, were randomised to receive either insulin detemir+liraglutide 1.8 mg+metformin or continued liraglutide 1.8 mg+metformin treatment (162 and 161 subjects, respectively).

A total of 25% of subjects withdrew during the entire period of the trial. The differences in withdrawal rates between the two randomised treatment groups were driven by ineffective therapy in the lira-control group. Of the total subject withdrawals, most subjects left the trial during the first 2 months of the run-in phase (22% for both months).

Overall, 75% of subjects completed the 38-week main trial period (run-in and main 26-week treatment period), with 26-week main trial completion rates being 88.9%, 78.9% and 94.4% for subjects in the detemir+lira group, lira-control group, and the non-randomised liraglutide 1.8 mg+metformin group, respectively.

For the extension study, 140 subjects (86.4%) in the detemir+lira group, 122 subjects (75.8%) in the lira-control group and 461 (92.6%) in the non-randomised group continuated treatment. Seventeen

(10.6%) of the subjects in the liraglutide-control group received insulin detemir intensification treatment, while in the non-randomized liraglutide 1.8 mg+metformin group seven (1.4%) subjects received this intensification treatment.

Overall, 68% of subjects completed the 64-week total trial period (12-week run-in, 26-week main treatment period and 26-week extension period), with completion rates being 80.2%, 57.1% and 85.5% for subjects in the detemir+liraglutide, liraglutide control and the non-randomised liraglutide 1.8 mg+metformin groups, respectively.

Recruitment

Study NN2211-1842 was conducted from the 3rd of March 2009 until the 19th of April 2010 (main period of 26 weeks).

Conduct of the study

Most important substantial protocol amendments:

There were 2 global and 16 local substantial amendments to the final protocol, version 1, dated 30 September 2008.

The substantial protocol amendments listed above are not expected to have had clinically relevant impact on the overall trial results.

Baseline data

The treatment groups were overall well matched with respect to baseline demographics and characteristics (see

Table 7). A slightly higher proportion of randomised subjects receiving liraglutide 1.8 mg+metformin were Black/African American (10.6%) compared to randomised subjects receiving insulin detemir+liraglutide 1.8 mg+metformin (4.9%).

Mean run-in efficacy parameters for subjects previously treated with metformin alone or sulphonylurea and metformin therapy demonstrated comparable results to those presented for all exposed subjects, although with generally lower means for HbA1c and FPG for subjects previously treated with sulphonylurea and metformin compared to with metformin alone.

Table 7: Summary of subject demographics and characteristics – All exposed subjects

		Lira-control	Detemir + Lira	All randomised
All exposed subjects, N		161	162	323
Age (years)*	Mean (SD)	57.3 (9.8)	56.8 (9.4)	56.5 (9.7)
	Median	58.0	57.0	57.0
	Min; Max	33.0; 79.0	31.0; 77.0	31.0; 79.0
Sex*, N (%)	Male	89 (55.3)	88 (54.3)	177 (54.8)
	Female	72 (44.7)	74 (45.7)	146 (45.2)
Weight (kg)**	Mean (SD)	95.32 (21.09)	95.99 (20.88)	
	Median	93.10	91.70	
	Min; Max	50.9; 174.0	49.9; 190.1	50.9; 190.1
BMI* (kg/m2)	Mean (SD)	33.9 (6.0)	34.9 (6.3)	34.4 (6.2)
	Median	33.0	33.5	33.2
	Min; Max	22.4; 60.6	22.6; 56.2	22.4; 60.6
Duration DM* (years)	Mean (SD)	8.5 (6.0)	8.6 (5.8)	8.5 (5.9)
	Median	7.5	7.7	7.7
	Min; Max	0.4; 30.5	0.4; 30.5	0.4; 30.5
Previous Treatment* (%)	metformin	81 (50.3)	81 (50)	162 (50.2)
	Metformin + SU	80 (49.7)	81 (50)	161 (49.8)
HbA1c (%)**	N	157	162	319
	Mean (SD)	7.64 (0.66)	7.63 (0.55)	
	Median	7.40	7.50	
	Min; Max	6.20; 10.10	7.00; 10.30	6.2; 10.3
FPG (mmol/L)**	N	155	160	315
	Mean (SD)	8.81 (2.10)	9.23 (1.86)	
	Median	8.60	9.00	
	Min; Max	5.20; 18.40	6.00; 17.10	5.2; 18.4

*** Values taken from first visit, before run-in period**
**** Values taken at baseline (Week 0)**

The screening physical examination findings were comparable across treatment groups (randomised and non-randomised) and most (about 90%) observations were normal for all organ systems.

Diabetic complications included neuropathy, retinopathy, nephropathy and macroangiopathy. The most frequent diabetic complications were neuropathy and retinopathy (reported by about 15% and 7% of subjects, respectively), while the overall prevalence of complications were comparable across treatment groups.

Nearly all subjects in all treatment groups reported concomitant illnesses (96.5%). The most frequent concomitant illnesses across treatment groups were disorders in the system organ class metabolism and nutrition disorders and related to hyperlipidaemia, hypercholesterolaemia, obesity and dyslipidaemia. The incidence of these events as well as the other events reported were comparable across treatment groups (both between randomised and for non-randomised).

Outcomes and estimation

Primary Endpoint – Change in HbA1c

Figure 2 illustrates that the greatest change in HbA1c in all treatment groups was observed during the 12-week run-in period; subjects in the randomised groups had a mean screening HbA1c of 8.3%, which decreased to 7.6% after the 12-week run-in period. A further significant decrease in HbA1c was observed from baseline to Week 12 for the detemir+lira group, after which HbA1c appeared to remain relatively stable. The estimated decrease in HbA1c from baseline to Week 26 was 0.51% in the detemir+lira group, whereas a small increase of 0.02% was observed in the lira-control group (comparing Least square means).

Figure 2: Mean HbA1c (%) from Run-in to Week 52 – No imputation – FAS and Non-randomized Treatment Groups (including values for intensified subjects in original treatment group)

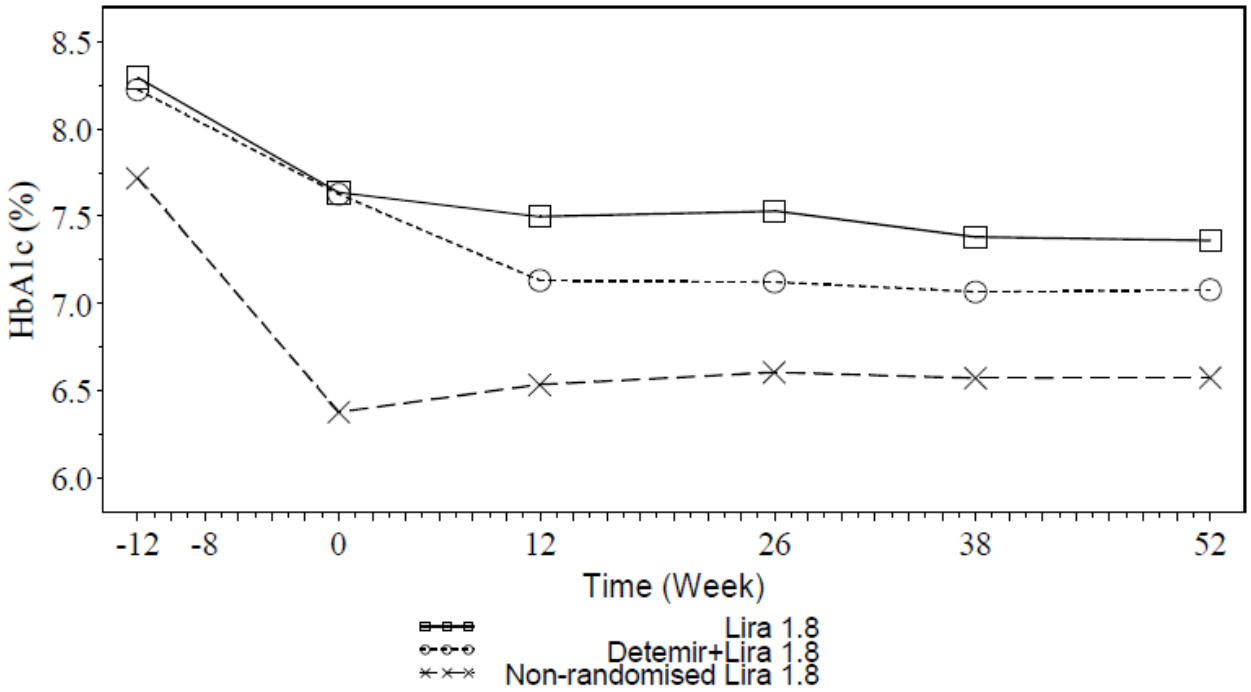


Table 8 shows the absolute values and change in HbA1c before the run-in period; at baseline (Week 0); at Week 26; and at Week 52.

Table 8: Summary of Absolute Values and Change in HbA1c (%) -FAS

		Lira-control*	Detemir + Lira
Week -12	N	157	162
	Mean (SD)	8.29 (0.82)	8.22 (0.74)
	Median	8.10	8.10
	Min; Max	6.10; 11.2	6.70; 10.50
Baseline: Week 0	N	157	162
	Mean (SD)	7.64 (0.66)	7.63 (0.55)
	Median	7.40	7.50
	Min; Max	6.20; 10.10	7.00; 10.30
Week 26	N	125	141
	Mean (SD)	7.53 (0.77)	7.12 (0.75)
	Median	7.40	7.00
	Min; Max	5.70; 9.80	5.50; 9.70
Change from baseline to Week 26	N	125	141
	Mean (SD)	-0.04 (0.68)	-0.51 (0.75)
	Median	0.00	-0.50
	Min; Max	-2.60; 1.70	-2.30; 1.90
Week 26, LOCF	N	149	160
	Mean (SD)	7.64 (0.87)	7.15 (0.75)
	Median	7.50	7.10
	Min; Max	5.70; 11.30	5.50; 9.70
Change from baseline to Week 26, LOCF	N	149	160
	Mean (SD)	0.03 (0.72)	-0.48 (0.73)
	Median	0.00	-0.50
	Min; Max	-2.60; 1.90	-2.30; 1.90
Week 52**	N	105	125
	Mean (SD)	7.36 (0.68)	7.08 (1.02)
	Median	7.30	6.80
	Min; Max	5.80; 9.70	5.40; 11.10
Change from baseline to Week 52**	N	105	125
	Mean (SD)	-0.20 (0.75)	-0.54 (0.94)
	Median	-0.10	-0.60
	Min; Max	-2.70; 2.00	-2.60; 2.80
Week 52, LOCF	N	149	160
	Mean (SD)	7.54 (0.89)	7.18 (1.00)
	Median	7.40	6.90
	Min; Max	5.40; 11.30	5.40; 11.10
Change from baseline to Week 52, LOCF	N	149	160
	Mean (SD)	-0.08 (0.82)	-0.45 (0.92)
	Median	0.00	-0.50
	Min; Max	-2.70; 2.70	-2.60; 2.80

***Including values for intensified subjects in original treatment group (at Week 52)**
****Completers only**

Results from the ANCOVA analysis demonstrates that treatment with insulin detemir+liraglutide 1.8 mg+metformin was superior to treatment with liraglutide 1.8 mg+metformin alone in terms of change in HbA1c from baseline to Week 26 (estimated treatment difference of -0.52%) (see Table 9). These results were further supported by a repeated measurements analysis of HbA1c levels after 12 and 26 weeks of randomised treatment.

Table 9: ANCOVA of change in HbA1c (%) – LOCF -FAS

Comparison of change from baseline after 26 weeks of treatment				
Treatment / Comparison	Estimates			Testing
Least Square Means	N	LSMean	SE	
Detemir+Lira 1.8	160	-0.51	(0.07)	
Lira 1.8	149	0.02	(0.07)	
Estimated Treatment Difference	LSMean	95% CI		P-value
Detemir+Lira 1.8 - Lira 1.8	-0.52	[-0.68 ; -0.36]		<.0001

All subjects also received metformin
The estimates are from an ANCOVA model with treatment, country and previous OAD as fixed effect and baseline value as a covariate

The mean change in HbA1c from randomisation to Week 52 was also analysed using an ANCOVA model including values for intensified subjects in the initial treatment group (HbA1c values used after intensification with detemir). In the FAS, using LOCF, the estimated mean changes in HbA1c from randomisation to Week 52 were -0.51% and -0.10% in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin treatment groups, respectively.

In order to elucidate the impact of the subjects who were exposed during the run-in period to less than 80 days before randomisation, both the summary tables showing the absolute values and changes in HbA1c by week and the planned ANCOVA on HbA1c was made for subjects with at least 80 days of exposure only. The mean changes over time were comparable to those observed for the treatment groups including the entire subject population, as were the ANCOVA estimated means and statistical significance levels. The inclusion of subjects with less than 80 days of exposure to liraglutide 1.8 mg + metformin prior to randomisation was therefore considered to have no impact on the overall results. No statistically significant interaction effect between treatment and either baseline HbA1c or baseline FPG was observed.

Secondary Endpoint – Proportion of Subjects Reaching HbA1c Targets

The proportion of subjects achieving pre-defined HbA1c targets (<7% target; and ≤6.5% target) at Week 26 is summarised in Table 10.

Table 10: Proportion of subjects with HbA1c <7% and ≤6.5% at Week 26 (LOCF) - FAS

	Lira 1.8			Detemir + Lira 1.8		
	N	n	(%)	N	n	(%)
Full Analysis Set	157			162		
Baseline HbA1c < 7.0 %	157	1	(0.6)	162	0	(0.0)
Week 26 HbA1c < 7.0 % #	125	29	(23.2)	141	65	(46.1)
Week 26 HbA1c < 7.0 % (LOCF)	149	30	(20.1)	160	71	(44.4)
Baseline HbA1c <= 6.5 %	157	1	(0.6)	162	0	(0.0)
Week 26 HbA1c <= 6.5 % #	125	10	(8.0)	141	28	(19.9)
Week 26 HbA1c <= 6.5 % (LOCF)	149	11	(7.4)	160	31	(19.4)

All subjects also received metformin
N = Number of subjects with non-missing value
n = Number of subjects reaching target
% = Percentage calculated as 100*n/N
# = Completers - No imputation method applied

The proportions of subjects achieving HbA1c <7% was greater with insulin detemir+liraglutide 1.8 mg+metformin compared to liraglutide 1.8 mg+metformin alone. The same was true for the number of subjects achieving the HbA1c ≤ 6.5% target.

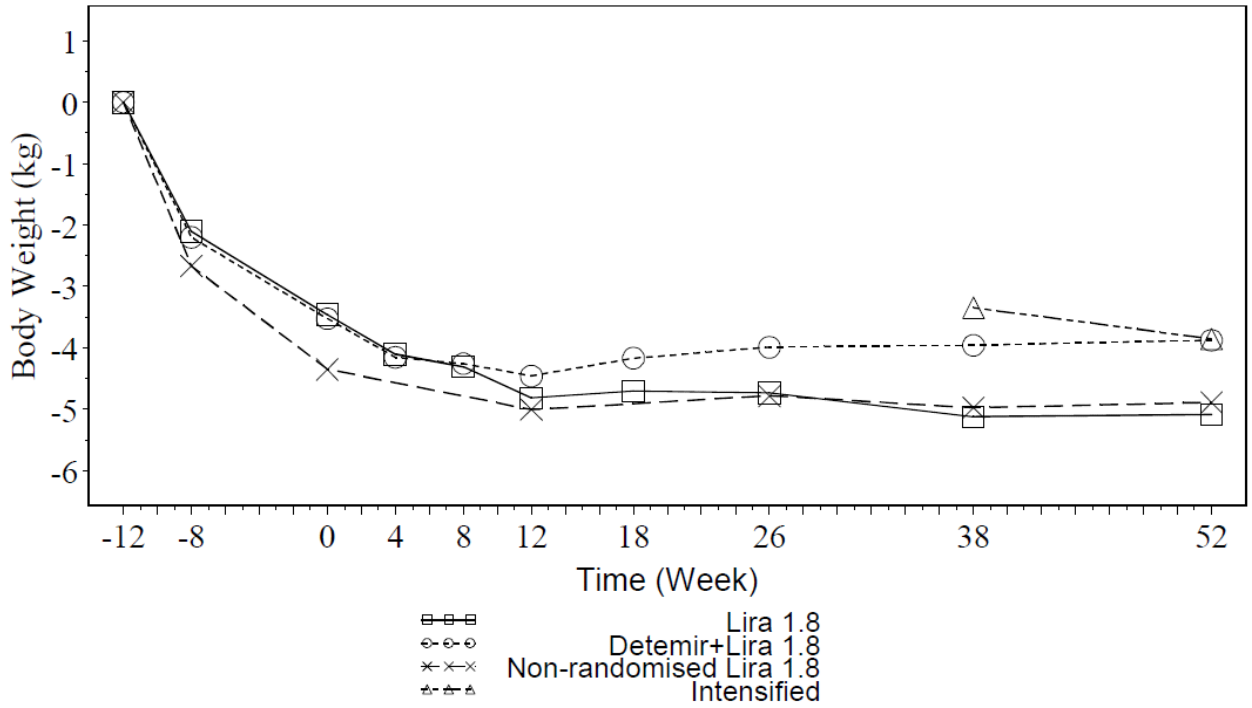
The proportion of subjects reaching targets was higher with insulin detemir+liraglutide 1.8 mg+metformin treatment compared to liraglutide 1.8 mg+metformin treatment, irrespective of baseline HbA1c level. Furthermore, the lower the baseline HbA1c level, the higher the proportion of subjects reaching targets.

The estimated proportions of subjects achieving HbA1c both <7.0% and ≤6.5% at Week 52 were in line with the Week 26 data. A significantly greater proportion of subjects with insulin detemir+liraglutide 1.8 mg+metformin treatment achieved these goals (51.9% and 22.4%) compared to subjects in the control group treated with liraglutide 1.8 mg+metformin (21.5% and 6.8%; including values before intensification as LOCF for intensified subjects) (p<0.0001 for both analyses).

Body weight

Mean body weight decreased by 3.5 to 4.3 kg during run-in. This weight loss was sustained throughout the main treatment period for subjects randomised to further intensification with insulin detemir (estimated mean change of -0.16 kg), whereas subjects continuing on liraglutide and metformin had a further estimated mean change of -0.95 kg (see Figure 3).

Figure 3: Mean change in body weight from run-in to Week 52 –No imputation - FAS



After 52 weeks, the difference between groups became slightly greater with an estimated mean change in body weight of -0.05 kg for the detemir+liraglutide group, versus -1.02 kg in the lira-control group (see Table 12). Table 11 shows the absolute body weight values at baseline, week 26 and end of the study (Week 52) and change in body weight from baseline to Week 26, and to week 52 using the Full Analysis Set without imputations. The mean body weight was numerically larger in the detemir+lira group, in comparison with the lira-control group, 95.99 kg vs 95.32 kg, although the median body weight shows the opposite, with values of 91.70 kg vs 93.10 kg, respectively. The SD of both the absolute value, and the difference in body weight from baseline, was rather large in the two treatment groups. Changes in body weight values, during this 52-week study, were between decreasing 15.4 kg, and gaining 13.2 kg. These minimum and maximum values were widely spread.

Table 11: Summary of absolute values and change in Body weight -FAS

Body weight (kg)		Lira	Detemir + Lira
Baseline: Week 0	N	157	162
	Mean (SD)	95.32 (21.09)	95.99 (20.88)
	Median	93.10	91.70
	Min; Max	50.90; 174.0	49.90; 190.1
Week 26	N	127	142
	Mean (SD)	94.14 (20.71)	95.25 (21.48)
	Median	91.50	90.00
	Min; Max	50.20; 168.6	50.80; 199.1
Change from baseline to Week 26	N	127	142
	Mean (SD)	-1.13 (3.17)	-0.31 (3.36)
	Median	-0.70	-0.10
	Min; Max	-14.6; 9.00	-12.4; 9.00
Week 52*	N	92	130
	Mean (SD)	93.80 (21.47)	93.12 (18.50)
	Median	91.45	89.65
	Min; Max	50.80; 168.6	50.80; 151.5
Change from baseline to Week 52*	N	92	130
	Mean (SD)	-1.35 (4.88)	-0.27 (4.40)
	Median	-1.75	0.20
	Min; Max	-15.4; 13.2	-16.0; 13.0

*** Completers only, intensified subjects are not included**

Table 12: ANCOVA of change in body weight (kg) at Week 52 – LOCF -FAS

Comparison of Change from Randomisation to Week 52

Treatment / Comparison	Estimates		
Least Square Means	N	LSMean	SE
Detemir+Lira 1.8	162	-0.05	(0.42)
Lira 1.8	157	-1.02	(0.41)

Estimated Treatment Difference	LSMean	95% CI	P-value
Detemir+Lira 1.8 - Lira 1.8	0.97	[0.04 ; 1.91]	0.0416

All subjects also received metformin
Last observation before intensification is used for LOCF of intensified Lira 1.8 mg subjects
The estimates are from an ANCOVA model with treatment, previous OAD and country
as fixed effect and baseline value as a covariate

Other secondary endpoints

Statistically significant improvements were seen in the detemir+lira group, in comparison with the lira-control group, during the 52 weeks of treatment for the following items:

- There was an estimated mean change in FPG of -2.12 mmol/L and -0.39 mmol/L, in the detemir+lira group and lira-control group, respectively ($p<0.0001$) at Week 26. At Week 52, the estimated mean change from baseline was -1.91 mmol/l and -0.14 mmol/l respectively, with an estimated treatment difference of (LS mean [95% CI]) -1.77 [-2.24; -1.30] mmol/L.
- Estimated mean decreases in post-prandial glucose at all meal times at Week 52, (ranging from -1.14 mmol/L to -2.43 mmol/L and -0.51 mmol/L to -0.96 mmol/L, for the two randomised treatments, respectively).
- Proportion of subjects (about 10% more) having post-prandial glucose measurements below 10 mmol/L at each meal at Week 26. At Week 52, only breakfast post-prandial glucose measurements showed a statistically significant difference between treatment groups. Although

no statistically significant treatment difference was observed for prandial glucose increments at either breakfast, lunch or dinner at either Week 26 or Week 52.

- A small, but greater number, difference for change in free fatty acids was seen at Week 26, estimated change of -0.11 mmol/L and -0.03 mmol/L (p=0.0017). However, no statistically significant difference was observed at Week 52.
- From randomisation to Week 52, there was a small statistically significant treatment difference for change in HDL-cholesterol in favour of detemir+lira group, with increases observed for both treatment groups (including values before intensification as LOCF for intensified subjects).
- At week 26, a greater proportion of subjects reaching the composite endpoint of HbA1c <7%, systolic blood pressure <130 mmHg and change in body weight ≤0kg, 10.5% and 4.1%, respectively (p=0.0126). Data at Week 52 were not provided by the MAH.
- At Week 26, a greater proportion of subjects reached the composite endpoint of HbA1c <7%, change in body weight ≤0kg and no major or minor hypoglycaemic episodes: 21.7% and 8.9%, respectively (p=0.0012). At Week 52, the proportions of subjects were 25.9% versus 16.8%. This difference between groups was at the end of the study no longer statistically significant (p=0.06).

No statistically significant differences were seen between the two treatment groups in fasting lipid profiles or blood pressure at Week 26 or Week 52.

Data on fasting insulin and hence HOMA-B and HOMA-IR could not be obtained for the insulin detemir+liraglutide 1.8 mg+metformin treated subjects due to cross-reactivity between insulin detemir and the insulin assay. Therefore, an overall effect of treatments on beta-cell function could not be established. Both pro-insulin and C-peptide levels decreased over time, where the decreases were statistically significantly greater for subjects in the detemir+lira group compared to subjects in the lira-control group (P=0.0230 and p<0.0001, respectively). Both mean baseline pro-insulin and baseline C-peptide values were slightly higher for subjects in the detemir+lira group. No treatment difference was observed for pro-insulin to C-peptide ratio.

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

To provide data on efficacy and safety of insulin detemir + metformin, the MAH submitted data from literature. Three sources were used:

Literature search

- An International Variability Evaluation (PREDICTIVE) search (PREDICTIVE™ is a global observational study including 30 countries following type 1 and type 2 DM patients initiated on Levemir. The primary objective of the study is to document the safety of using Levemir)
- All available Levemir clinical trials were used to identify patients with comparable patient populations.
- The MAH identified comparable patient populations in the above mentioned studies/literature to provide data on efficacy and safety of the basal insulin and metformin combination.

Results from these searches are shown in Table 13.

The literature search provided two articles: Meneghimi et al. and Selam et al. Both articles described the PREDICTIVE study. This PREDICTIVE 303 Trial included 5604 DM type 2 patients with HbA1c ≤12%. Age (58.6 years), weight (97.8 kg) and diabetes duration (11.4 years) were comparable with

study NN2211-1842, but HbA1c levels and previous diabetes treatment were different from study NN2211-1842.

HbA1c levels in the PREDICTIVE study were up to 12% without cut off point for minimum value. A third of the population (30.6%) had an HbA1c level >9.0%; and there was a group of patients (13.3%) with a baseline HbA1c level below 7%. The pre-treatment in this population included all possible varieties. A third of the patients (32%) used OADs only, while a large group (43%) was on insulin at baseline, and a small fraction (2.3%) did not receive any treatment at baseline (ref.: Meneghini et al).

A post hoc sub-analysis was performed in 1806 insulin-naïve patients participating in the PREDICTIVE study by Selam et al. On average patients were taking two OADs. Metformin was most commonly used (72%), followed by SU (70%) and TZD (55%). A third (33.4) of these subjects had an HbA1c above 9%, and a group of 10.9% had an HbA1c <7%. The subjects participating in this PREDICTIVE trial were not on insulin detemir in combination with metformin.

The MAH selected 238 patients from the PREDICTIVE study who were on insulin detemir + metformin during the trial. Again, the age (58.5 years), weight (93.5 kg) and diabetes duration (10.3 years) were comparable with study NN2211-1842. However the mean baseline HbA1c, 8.85%, and the previous treatment were different from study NN2211-1842. A large proportion (60.50%) of the subjects was on metformin only, while 19.75% used the combination of metformin+SU (dosage not known). Eight subjects (3.4%) did not receive any treatment at baseline. About a third of this population used other forms of OAD medication, including triple therapy. Insulin dosage at baseline was 0.32U/kg, in contrast to study NN2211-1842 where only insulin naïve patients participated.

Furthermore, the MAH gathered 76 subjects on detemir + metformin treatment from three pooled Levemir Trials. These patients had a higher mean HbA1c at baseline (8.72%), body weight was slightly lower (91.55 kg), while the previous diabetes treatment was not mentioned. During the trials, change in HbA1c was -1.88% and mean body weight increased with 0.74kg. Hypoglycaemic episodes were found in eight (10.5%) patients, with in total 20 events.

Table 13: Overview of the supportive data in subjects treated with basal insulin and metformin (HbA1c, body weight, insulin dose, and hypoglycaemic episodes)

Data Included	Number Subjects	Treatment Duration	Treatment	HbA_{1c} (%)	Insulin dose (U/kg)	Body Weight (kg)	Hypoglycaemic Episodes (event/patient/year)
Trial 1842	987	26	Insulin detemir + liraglutide 1.8 mg + metformin (N=162)	Weeks -12 and 0: 8.22, 7.63 Week 26: 7.15 Change from run-in: -1.13 Change from Week 0#: -0.51	Week 26: 0.41	Weeks -12 and 0: 99.52, 95.99 Week 26: 95.66 Change from run-in: -4.0 Change from Week 0#: - 0.16	Minor*0.247 Major: 0
			liraglutide 1.8 mg + metformin (N=157)	Weeks -12 and 0: 8.29, 7.64 Week 26: 7.64 Change from run-in: -0.76 Change from Week 0#: 0.02	Not applicable	Weeks -12 and 0: 98.78, 95.32 Week 26: 94.19 Change from run-in: -4.74 Change from Week 0#: -0.95	Minor: 0.029 Major: 0 (26-week period)
Supportive Data: Literature Search							
Meneghini[9]	5604	26	303 algorithm Insulin detemir add/on or switch	Baseline: 8.5 Week 26: 7.9 Change: -0.6	Baseline: 0.32 Week 26: 0.68	Baseline: 97.0 Week 26: 97.0 Change# : 0.1	All: 6.44 Major: 0.26
			physician standard of care Insulin detemir add/on or switch	Baseline: 8.5 Week 26: 8.0 Change: -0.5	Baseline: 0.34 Week 26: 0.53	Baseline: 98.2 Week 26: 97.9 Change# : -0.2	All: 4.95 Major: 0.20
Selam[10]	1806	26	303 algorithm Insulin detemir/OAD (insulin-naïve)	Baseline: 8.7 Week 26: 7.6 Change: -1.1	Week 26: 0.59	Baseline: 96.7 Week 26: 97.9 Change#: 1.1	All: 3.46 Major: 0.08
			physician standard of care (insulin naïve)	Baseline: 8.6 Week 26: 7.7 Change: -1.0	Week 26: 0.40	Baseline: 98.4 Week 26: 98.6 Change#: 0.4	All: 3.14 Major: 0.03
Supportive Data: PREDICTIVE Search							
PREDICTIVE Search	238	26	Insulin detemir + metformin	Baseline: 8.85 Week 26: 8.14 Change: -0.70	Baseline: 0.32 Week 26: 0.57	Baseline: 92.6 Week: 92.0 Change: 0.7	Major: 2
Supportive Data: Pooled Levemir® Trials 1373, 1530 and 1632 (Weeks 28, 24 and 20, respectively)							
Pooled Trials ***	76	28, 24 and 20	Insulin detemir + metformin	Baseline: 8.72 Week 28, 24, 20: 6.84 Change: -1.88	Week 28, 24, 20: 0.68	Baseline: 91.55 Week 28, 24, 20: 92.05 Change: 0.74	Minor**: 0.593 Major: 0

The MAH stated that all the data presented for subjects treated with basal insulin + metformin illustrate that the change in HbA1c observed in these populations was associated with a net weight gain and a higher incidence of hypoglycaemic episodes compared to what was observed in study NN2211-1842. Finally, there was a general need for higher doses of insulin (0.41U/kg versus 0.68 U/kg), i.e. up to 40% more per kg body weight compared to both Meneghini et al and the pooled Levemir trials to achieve a clinically relevant reduction in HbA1c, compared to that used by subjects receiving insulin detemir + liraglutide 1.8 mg + metformin in the study.

Therefore, these data support the efficacious combination of basal insulin, liraglutide and metformin, where liraglutide contributes to the efficacy with less basal insulin required (units/kg), a net weight loss or weight neutrality and a lower incidence of hypoglycaemic episodes.

1.2.5. Discussion on clinical efficacy

The MAH claimed an extension of the indication for Victoza in the treatment of T2DM in combination with basal insulin in patients not achieving glycaemic control with Victoza and metformin alone. This was not considered as acceptable by the CHMP, as this would be more an indication for insulin detemir. For an indication for Victoza, it should be demonstrated that liraglutide has a value in efficacy and safety when added to insulin. The design of study NN2211-1842 only gives information about the efficacy and safety of insulin detemir when added to metformin + liraglutide. The design does not allow for a conclusion about the added value of liraglutide in this combination. In the study design, an extra treatment arm with the treatment combination of insulin detemir + metformin is missing. The MAH submitted a total of two trials, a pooled trial and a data set with type 2 diabetes patients using the combination of detemir insulin plus metformin. The idea behind this comparison with subjects included in study NN2211-1842 was to create an imaginary treatment arm in this study. In this way, assessment of the efficacy and safety of liraglutide itself in the treatment combination with insulin detemir might be possible. However, the study populations are different in terms of pre-existing

metabolic control, severity of diabetes, and pre-study medication. Therefore, this additional data is not really helpful in the assessment of the efficacy of liraglutide in the combination treatment. Nevertheless, the CHMP considered it important for the prescribing physicians to have access to information reflecting the trial results in the Victoza SmPC in section 5.1.

In the randomised groups, addition of insulin detemir on top of the combination therapy metformin + liraglutide showed a clinically relevant estimated mean change in HbA1c from baseline to Week 26 of -0.51% in this study. Mean change (SD) of HbA1c from baseline to Week 26 without imputations resulted in -0.04% (0.68), vs -0.51% (0.75), for lira-control group vs. the detemir+lira group, a difference of -0.47%. This is comparable to the difference measured with LOCF.

52 Week data were provided by the MAH. The efficacy data of this 26-Week extension study were in line with the main 26-Week efficacy data. The effect on HbA1c was sustained. As expected, a larger proportion of subjects in the detemir+lira group achieved HbA1c goals of <7% and ≤6.5%, in comparison with the lira-control group. This difference was clinically relevant.

Body weight dropped in both treatment groups, with statistically significant difference between groups in favour of the lira-control group, indicating less reduction in body weight when insulin is added to liraglutide. The reduction in body weight, between baseline (Week 0), Week 26 and Week 52, was however small, and the SD is quite large.

All secondary endpoints are in line with the primary, HbA1c, results. However, all secondary endpoints were only of supportive evidence to the primary endpoint since no adjustment for multiplicity was applied in the analyses of the secondary endpoints.

Lower number of patients in the lira-control group completed the study: 57.1%, versus 80.2% in the detemir+lira group. Half of the withdrawals in the randomised liraglutide+metformin arm were due to withdrawal criteria (pregnancy; confirmed fasting plasma glucose exceeding 11.1mmol/l (200 mg/dL) after randomisation; suspicion of acute pancreatitis. Though a higher number of withdrawals in the randomised liraglutide+metformin arm based on poor glycaemic control would have been expected, no details have been provided regarding the distribution of withdrawal criteria. Data was provided regarding the withdrawals from all treatment groups. The number of withdrawals by reason and by week since randomisation did not signal a specific pattern in between the three treatment groups. Neither did the graphical presentations by withdrawal reason and by week since randomisation cause any concerns.

There were no statistically significant differences in systolic or diastolic blood pressure between the two randomised treatment arms seen from randomisation to end of study. The MAH demonstrated that the reduction of systolic blood pressure seen in the original dossier of liraglutide was in line with the results from study NN2211-1842 when the run-in (start liraglutide) was taken into account. In study NN1122-1842, systolic blood pressure reductions were between 1.6 and 6.3 mmHg from run-in to 52 weeks treatment. In the interim 6-months data, blood pressure lowering effects of liraglutide between 2.3 and 6.7 mmHg were observed. However, the systolic blood pressure reduction was numerically larger in patients treated with liraglutide + metformin compared to patients treated with liraglutide + metformin + insulin detemir.

According to the data on blood pressure in the original dossier, liraglutide decreased the systolic blood pressure on average of 2.3 to 6.7 mmHg from baseline and compared to active comparator the decrease was 1.9 to 4.5 mmHg over the duration of studies. This effect is in contrast to the results obtained in study NN2211-1842; though a decrease of 1.34 mmHg was observed from run-in to end of treatment (completers) for non-randomised subjects. An increase in systolic blood pressure was observed for the same period for the randomised lira-control group, an increase that was in fact numerically higher than that observed for the detemir+lira group.

Furthermore, metformin treatment was not provided by the sponsor. It was confirmed that appropriate actions were taken during the study to ensure compliance to metformin treatment. The mean dose of metformin was comparable between groups (2045.3 mg in the lira-control group, versus 2129.8 mg in the detemir+lira group).

1.2.6. Conclusions on clinical efficacy

The triple therapy regimen (insulin detemir + liraglutide + metformin) had a statistically significant lowering effect on HbA1c after 26 weeks of treatment when compared to dual therapy (liraglutide + metformin). This effect was further supported by a statistically significantly higher number of subjects reaching the predefined HbA1c targets of < 7.0% and 6.5% respectively. However study NN2211-1842 was designed to determine the efficacy of adding insulin determir to the therapy of T2DM patients whose glucose levels are not sufficiently controlled on the combination treatment of liraglutide 1.8 mg and metformin. The impact of liraglutide in this triple combination is not known and therefore the benefit of Victoza in this triple combination has not been demonstrated.

1.2.7. Clinical safety

Patient exposure

A total of 987 subjects were exposed to trial products. After the run-in period 39.3% of the subjects (n=323) were inadequately controlled with the combination therapy liraglutide 1.8mg + metformin and underwent randomisation to either insulin detemir+liraglutide 1.8 mg+metformin or liraglutide 1.8 mg+metformin alone.

The subject exposure to trial products is summarised in Table 14 and reflects the percentages in the randomised and non-randomised treatment groups. The greatest liraglutide exposure was in the non-randomised liraglutide 1.8 mg+metformin group, with a mean duration of 427 days. For the two randomised treatment groups, mean duration of liraglutide treatment was slightly longer (42 days) in subjects in the detemir+lira group (411 days) versus that for subjects in the lira-control group (369 days), as also reflected in the greater total subject exposure time. Mean duration of insulin detemir treatment was about 326 days with a total subject exposure time of 145 years for subjects in the detemir+lira group.

Table 14: Summary of exposure to trial drugs – All Exposed Subjects

	Lira 1.8	Detemir + Lira 1.8	Non-randomised Lira 1.8	Intensified*	All
Safety Analysis Set	142	163	492	24	821
Duration of Liraglutide Treatment (days)					
N	142	163	492	24	821
Mean (SD)	369.3 (124.1)	411.3 (93.1)	426.5 (73.6)	446.3 (38.8)	414.1 (90.1)
Median	448.0	449.0	449.0	453.0	449.0
Min ; Max	92.0 ; 489.0	89.0 ; 495.0	83.0 ; 500.0	269.0 ; 480.0	83.0 ; 500.0
Total lira exposure in subject years **	143.6	183.6	574.4	29.3	930.9
Duration of Detemir Treatment (days)					
N		162		24	186
Mean (SD)		325.7 (90.0)		152.1 (46.1)	303.3 (103.6)
Median		364.0		173.5	362.5
Min ; Max		28.0 ; 406.0		2.0 ; 186.0	2.0 ; 406.0
Total detemir exposure in subject years**		144.5		10.0	154.5

* Intensified subjects are tabulated in Intensified group only
** One patient year equals 365.25 days

For subjects randomised to insulin detemir+liraglutide 1.8 mg+metformin, insulin detemir was initiated at a dose of 10 U, with further titration at visits depending on the subjects' self-measured plasma glucose levels. The mean prescribed dose was 0.41 U/kg and 0.45 U/kg for these subjects at Week 26 and Week 52 respectively.

Adverse events

A summary of adverse events by treatment is presented in Table 15. The proportion of subjects reporting adverse events was comparable between the two randomised treatment groups and also for the non-randomised treatment group. The incidence of adverse events with probable, possible or unlikely relation to treatment was comparable across the two randomised treatment groups and the non-randomised treatment group, as were the incidences of mild, moderate and severe events. The majority of adverse events was mild in severity and thought to be unlikely related to trial products.

Table 15: Summary of treatment emergent adverse events –Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early Withdrawals		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24			166		
Intensified	17						7			24					
All Adverse Events	124	(78.0)	716	132	(81.0)	845	433	(86.8)	2389	14	(58.3)	30	122	(73.5)	383
Serious Adverse Events	11	(6.9)	16	17	(10.4)	21	62	(12.4)	79	1	(4.2)	1	6	(3.6)	6
Relation to Treatment Regimen															
Probable	42	(26.4)	87	42	(25.8)	95	156	(31.3)	406	3	(12.5)	3	81	(48.8)	195
Possible	59	(37.1)	128	53	(32.5)	124	187	(37.5)	401	5	(20.8)	5	48	(28.9)	98
Unlikely	109	(68.6)	493	122	(74.8)	618	385	(77.2)	1563	10	(41.7)	22	46	(27.7)	82
NA	6	(3.8)	8	7	(4.3)	8	15	(3.0)	19				6	(3.6)	8
Severity															
Severe	14	(8.8)	19	17	(10.4)	19	52	(10.4)	67	1	(4.2)	1	31	(18.7)	41
Moderate	66	(41.5)	164	73	(44.8)	212	229	(45.9)	552	8	(33.3)	11	75	(45.2)	176
Mild	111	(69.8)	533	117	(71.8)	614	393	(78.8)	1770	12	(50.0)	18	72	(43.4)	166

All subjects also received metformin
AEs of intensified subjects are tabulated in initial treatment group if the AE occur before intensification. If the AE increase in severity after intensification it will be tabulated in both treatment groups
N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

The most commonly reported adverse events in all treatment groups and for the entire trial period was nasopharyngitis within the system organ class infections and infestations: 20%, 25% and 14% of subjects in the detemir+liraglutide, liraglutide-control and the non-randomised treatment groups, respectively (see Table 16). Gastrointestinal disorders, mostly nausea, diarrhoea and vomiting were also common in all treatment groups. Increased lipase was reported by a higher proportion of subjects in the detemir+lira group versus both the randomised and non-randomised liraglutide 1.8 mg+metformin groups (16.0% versus 10.1% and 11.0%). Generally, the proportion of subjects reporting adverse events was comparable across the two randomised treatment groups and the non-randomised treatment group.

During the extension phase of study NN2211-1842, seven (7) cases (4.3%) of neoplasms were identified in the detemir+lira group, while one (1) was reported in the liraglutide-control group and twelve (12) neoplasms (2.4%) in the non-randomised liraglutide + metformin group. There was no apparent clustering in the types of neoplasm seen in the detemir+lira group.

Table 16: Treatment emergent adverse events with an incidence ≥ 5% of subjects in any treatment by System Organ Class and Preferred term – Safety Analysis Set

	Lira 1.8 N	(%)	E	Detemir + Lira 1.8 N	(%)	E	Non-randomised Lira 1.8 N	(%)	E	Intensified N	(%)	E	Early Withdrawals N	(%)	E
Safety Analysis Set	159			163			499			24			166		
Intensified	17						7			24					
All Adverse Events	124	(78.0)	716	132	(81.0)	845	433	(86.8)	2389	14	(58.3)	30	122	(73.5)	383
Gastrointestinal disorders	74	(46.5)	182	77	(47.2)	202	241	(48.3)	696	3	(12.5)	4	98	(59.0)	212
Diarrhoea	26	(16.4)	29	29	(17.8)	42	74	(14.8)	108	1	(4.2)	1	21	(12.7)	25
Nausea	37	(23.3)	51	30	(18.4)	40	136	(27.3)	204	1	(4.2)	1	66	(39.8)	72
Vomiting	19	(11.9)	21	17	(10.4)	26	50	(10.0)	113				21	(12.7)	25
Dyspepsia	8	(5.0)	11	10	(6.1)	11	42	(8.4)	54				33	(19.9)	42
Constipation	11	(6.9)	11	8	(4.9)	10	25	(5.0)	30				11	(6.6)	11
Abdominal Pain	8	(5.0)	11	6	(3.7)	7	14	(2.8)	17				5	(3.0)	6
Infections and infestations	74	(46.5)	140	72	(44.2)	153	196	(39.3)	352	4	(16.7)	5	8	(4.8)	10
Nasopharyngitis	40	(25.2)	57	33	(20.2)	45	72	(14.4)	97	3	(12.5)	3	2	(1.2)	2
Upper Respiratory Tract Infection	9	(5.7)	14	13	(8.0)	13	21	(4.2)	24						
Nervous system disorders	38	(23.9)	74	35	(21.5)	84	123	(24.6)	241	2	(8.3)	2	21	(12.7)	34
Headache	23	(14.5)	41	21	(12.9)	54	73	(14.6)	144	2	(8.3)	2	13	(7.8)	22
Investigations	34	(21.4)	58	42	(25.8)	66	109	(21.8)	163	4	(16.7)	4	14	(8.4)	18
Lipase Increased	16	(10.1)	17	26	(16.0)	27	55	(11.0)	60	4	(16.7)	4	6	(3.6)	7
General disorders and administration site conditions	22	(13.8)	35	31	(19.0)	62	81	(16.2)	114	1	(4.2)	1	25	(15.1)	31
Fatigue	9	(5.7)	10	12	(7.4)	13	15	(3.0)	16				6	(3.6)	8
Musculoskeletal and connective tissue disorders	33	(20.8)	47	27	(16.6)	53	115	(23.0)	182	3	(12.5)	3	9	(5.4)	11
Back Pain	10	(6.3)	10	4	(2.5)	6	26	(5.2)	30	1	(4.2)	1	4	(2.4)	5
Respiratory, thoracic and mediastinal disorders	24	(15.1)	34	26	(16.0)	34	69	(13.8)	92				4	(2.4)	4
Oropharyngeal Pain	10	(6.3)	11	5	(3.1)	5	17	(3.4)	19				2	(1.2)	2
Metabolism and nutrition disorders	17	(10.7)	19	19	(11.7)	20	66	(13.2)	72	1	(4.2)	1	19	(11.4)	19
Decreased Appetite	9	(5.7)	9	13	(8.0)	13	50	(10.0)	53				17	(10.2)	17

All subjects also received metformin
AEs of intensified subjects are tabulated in initial treatment group if the AE occur before intensification. If the AE increase in severity after intensification it will be tabulated in both treatment groups
N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

Serious adverse events and deaths

There were no deaths reported during the main period of the trial. However, two deaths were reported during the 26-week extension trial, both within the system organ class neoplasms benign, malignant and unspecified, and both were rated as unlikely to be related to treatment. One death was due to pulmonary mass and metastases to the central nervous system (randomised liraglutide 1.8 mg + metformin) and the other death was due to gallbladder cancer and metastases to liver (nonrandomised liraglutide 1.8 mg + metformin).

The proportion of subjects reporting serious adverse events during the 52-Week trial was overall comparable across treatment groups (10.4%, 6.9% and 12.4% for subjects in the detemir+liraglutide group, liraglutide-control group and non-randomised liraglutide 1.8 mg+metformin, respectively see Table 17). A total of 123 serious adverse events were reported by 97 subjects (including 'early withdrawals') in the entire trial period. For all treatments, most events were unlikely related to trial products and severe in nature. No pattern or clustering of events was observed during the main period of the trial (week 0-26), with most events being reported by single subjects only and spread across several system organ classes. During the 26-week extension period, the most frequently reported adverse events were within the system organ class neoplasms, benign, malignant and unspecified (including cysts and polyps). These were reported by 4 subjects (2.5%) in the detemir+lira group and 3 subjects (0.6%) in the non-randomised liraglutide 1.8 mg + metformin treatment group (see below under "*Neoplasm related adverse events*").

Table 17: Summary of serious treatment emergent adverse events during the 52-Week study –Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early Withdrawals		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24			166		
Intensified	17						7			24					
Serious Adverse Events	11	(6.9)	16	17	(10.4)	21	62	(12.4)	79	1	(4.2)	1	6	(3.6)	6
Relation to Treatment Regimen															
Possible	4	(2.5)	4				6	(1.2)	6				2	(1.2)	2
Unlikely	8	(5.0)	11	17	(10.4)	21	56	(11.2)	73	1	(4.2)	1	4	(2.4)	4
NA	1	(0.6)	1												
Severity															
Severe	7	(4.4)	9	8	(4.9)	10	33	(6.6)	38	1	(4.2)	1	5	(3.0)	5
Moderate	3	(1.9)	5	11	(6.7)	11	25	(5.0)	30						
Mild	2	(1.3)	2				10	(2.0)	11				1	(0.6)	1

All subjects also received metformin
N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events
AEs of intensified subjects are tabulated in initial treatment group if the AE occur before intensification. If the AE increase in severity after intensification it will be tabulated in both treatment groups

Adverse Events Leading to Withdrawal of Subjects

In total, 127 out of 987 subjects (12.9%) exposed to liraglutide withdrew or were withdrawn from the trial due to adverse events. A total of 92 subjects withdrew before the randomisation visit (‘early withdrawals’), while 7 subjects (4.3%) of the detemir+liraglutide, 9 subjects (5.6%) of the liraglutide-control group, and 19 subjects (3.8%) in the non-randomised group withdrew after randomisation. No treatment difference or clustering in type of adverse event withdrawals were observed. The reasons for withdrawing for the seven subjects out of the detemir+lira group were (all items were mentioned for one subject only): increased lipase; increased pancreatic enzymes; abdominal pain with diarrhoea; gastric carcinoma; convulsion; renal failure; and bronchopulmonary disease.

Hypoglycaemia

One (1) subject experienced 24 episodes of minor and symptoms-only hypoglycaemia; this subject was identified as an outlier prior to database lock for the 26-week main period of the trial and was excluded from the analyses.

The rate of minor and symptomatic only hypoglycaemic episodes reported during the main and the extension period was compared for the two randomised treatment groups in Table 18. Overall, the rate of minor hypoglycaemic episodes was low across all treatment groups, at 0.228, 0.034 and 0.115 events per subject year for the detemir+liraglutide, liraglutide-control and the non-randomised liraglutide group, respectively. A similar pattern was evident for ‘symptoms only’ hypoglycaemic episodes, with the highest rate being reported for subjects in the detemir+liraglutide group (0.394 events per subject year), followed by subjects in the liraglutide-control (0.119) and non-randomised (0.091) treatment groups.

The rate of both all episodes and minor hypoglycaemic episodes was significantly higher in the insulin detemir + liraglutide 1.8 mg + metformin treated subjects compared to the liraglutide 1.8 mg + metformin treated subjects (p=0.0012 and p=0.0011, respectively). When including this outlier, no statistically significant treatment differences were observed. The number of subjects reporting both all hypoglycaemic episodes and minor episodes was significantly higher in the detemir+lira group compared to the lira-control group (p=0.0009 and p=0.0017, respectively). No statistically significant treatment difference was observed for the number of subjects reporting hypoglycaemic episodes classified as symptoms only.

Table 18: Analysis of hypoglycaemic episodes during main and extension period (excluding outlier*)–Safety Analysis Set

	Rate Ratio (Detemir+Lira 1.8 / Lira 1.8)		
Treatment / Comparison	Estimates	95% CI	P-value
All Episodes			
Detemir+Lira 1.8 / Lira 1.8	4.13	[1.75 ; 9.73]	0.0012
Minor Episodes			
Detemir+Lira 1.8 / Lira 1.8	6.80	[2.14 ; 21.60]	0.0011
Symptomatic Episodes			
Detemir+Lira 1.8 / Lira 1.8	2.65	[0.78 ; 8.97]	0.1174

All subjects also received metformin
Intensified Lira 1.8 subjects have intensified period excluded from analysis
Subject 916005 is an outlier and excluded due to extreme number of hypos
The estimated rate of episodes are from a negative binomial model with treatment and pervious OAD as fixed effect
The model is not estimable for major and unknown episodes

* One subject, a 57-year-old female, reporting 24 minor and symptoms only hypoglycaemic episodes was identified as an outlier prior to database lock for the 26-week main period of the trial. The first episode was reported prior to trial drug start during the screening phase (symptoms only, blood glucose 3.3 mmol/L). The next event occurred after 16 days of liraglutide and metformin treatment. The subject had a history of hypoglycaemia since 2007, which was specified as ongoing at the time of screening. When including this outlier, no statistically significant treatment differences were observed.

Neoplasm related adverse events

A summary of neoplasm adverse events reported during the 12-week run-in, 26-week main trial and 26-week extension period is presented in Table 19. Twenty-one (21) neoplasm adverse events were reported by 20 subjects. The number of events was small and most events were reported by single subjects only. No clustering in the types of neoplasms reported was observed. Of the 21 events reported, 11 were serious and 3 led to trial product withdrawal. Eleven (11) of the subjects fully recovered or were recovering at time of reporting.

Table 19: Neoplasm Related Treatment Emergent Adverse Events Classified as MESIs by System Organ Class and Preffered Term – Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early Withdrawals		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24			166		
Intensified	17						7			24					
All Adverse Events	1	(0.6)	1	7	(4.3)	7	12	(2.4)	13				2	(1.2)	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.6)	1	7	(4.3)	7	12	(2.4)	13				2	(1.2)	2
B-Cell Lymphoma				1	(0.6)	1									
Basal Cell Carcinoma				1	(0.6)	1									
Breast Cancer				1	(0.6)	1									
Fibroadenoma Of Breast				1	(0.6)	1									
Lung Squamous Cell Carcinoma Stage Unspecified				1	(0.6)	1									
Oesophageal Carcinoma				1	(0.6)	1									
Squamous Cell Carcinoma Of Skin				1	(0.6)	1									
Fibrous Histiocytoma							1	(0.2)	1						
Gallbladder Cancer							1	(0.2)	1						
Gastric Cancer							1	(0.2)	1						
Lipoma							1	(0.2)	1						
Metastases To Central Nervous System	1	(0.6)	1												
Metastases To Liver							1	(0.2)	1						
Prostate Cancer							1	(0.2)	1						
Renal Cancer							1	(0.2)	1						
Skin Papilloma							1	(0.2)	1						
Thyroid Cancer													1	(0.6)	1
Thyroid Neoplasm							3	(0.6)	3				1	(0.6)	1
Uterine Leiomyoma							2	(0.4)	2						

All subjects also received metformin
AEs of intensified subjects are tabulated in initial treatment group if the AE occurs before intensification. If the AE increases in severity after intensification it will be tabulated in both treatment groups
N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

Following the reporting of 7 cases of neoplasms in the triple combination arm (insulin detemir + liraglutide + metformin) during the extension phase of study NN2211-1842, the MAH was requested by the CHMP to justify that that the triple combination can be used safely and to discuss possible mechanisms and ways to further elucidate this concern. To address this concern the MAH provided the following:

- An exploration of study NN2211-1842 data-set for any indication of a tumour growth promoting effects in the triple combination arm by considering all treatment emergent AEs.
- All narratives and additional clinical information as well as follow-up information to enable a comprehensive overview of the potential additional risk factors identified for each event. For all the malignant neoplasms, further evaluation of confounding risk factors was done.
- A statistical (post-hoc) analysis of the neoplasm events (total and malignant cases alone) including several sensitivity analyses for evaluation of statistical differences between the treatment groups.
- In a separate statistical sub-analysis, the NN2211-1842 data have been investigated for any significant difference between the two treatments (insulin detemir + liraglutide + metformin and liraglutide + metformin) in the development of a new neoplasm among subjects with a previous event of neoplasms according to their medical history. This was done in order to further disclose any potential tumour growth promoting effect of the triple combination therapy.
- Based on non-clinical and clinical data, discussion on any possible mechanisms for tumourgenicity and a tumour growth promoting effect of insulin and liraglutide, both individually and combined
- Potential actions to further elucidate and ensure ongoing surveillance regarding this concern.

The MAH provided extensive narrative information. There were 6 patients with malignant neoplasms in the triple combination arm, of which one, however, had a wrong date of onset (event occurred before administration of insulin detemir) which leaves 5 patients with malignant event. In the randomised lira+met arm there was 1 patient with a malignant neoplasm and in the non-randomised lira+met arm arm there were 5 malignant events in 4 patients. The proportion of malignant events was thus distinctly higher in the triple combination arm (5/163; 3.1%) compared to the randomised control arm (1/159; 0.6%) or compared to the pooled lira+met arms (5/658; 0.8%). The MAH stated that the larger drop-out rate in the randomised and non-randomised control group accounted for relatively higher numbers of neoplasms in the triple therapy group. Taking these withdrawals into account, the proportion of malignant neoplasms would be 3.85% (5/[162-32]) in the insulin detemir + liraglutide + metformin group, compared to 0.79% (1/[161-53]) in the randomised control group, and 0.74% (4/[(161-53)+(498-66)]) in the pooled liraglutide + metformin group. In conclusion, even after correction of withdrawal rates and removing the patient who developed malignant neoplasm before starting the triple therapy, there is a higher proportion of malignant cases in the insulin detemir + liraglutide + metformin group compared to the control groups in study NN 2211-1842.

No contributing risk factors could be identified for the malignancy in the randomised liraglutide+metformin arm. Among the 4 subjects with malignant events in the non-randomised arm the MA identified 2 patients with potentially contributing/risk factors.

The majority of the malignant cases was confounded by strong risk factors and contributing factors for cancer and that there were few”un-explained” malignant neoplasms. However, an alternative explanation could still be the promotion of the malignant tumours by the detemir/liraglutide treatment in patients with risk factors. This can not be rule out at the moment.

None of the conducted post-hoc statistical analyses supported the concern regarding a growth promoting effect of the triple combination treatment. However, the most important test showed an estimated OR for reporting a malignant neoplasm related TEAE between the two randomised treatment arms of 5.0 with a 95% CI [0.58; 43.28], without taking the falsely included malignant case in the triple group into account. Since the CI contained the "1", no statistically significant difference was shown, but numbers are too low for any statistical conclusions.

The growth promoting effect was also not suggested by the non-clinical data. Long-term carcinogenicity studies with metformin have been performed in rats (≤900 mg/kg/day for 104 weeks) and in mice (≤1500 mg/kg/day for 91 weeks). No evidence of carcinogenicity was found in male or female mice or in male rats.

Standard carcinogenicity studies were not performed with insulin detemir. Insulin detemir has a slightly lower affinity than insulin itself for the insulin receptors (IR-A and IR-B) and the insulin-like Growth Factor-1 (IGF-1) receptor. Especially the IGF-1 receptor has been linked to the mitogenic effects of insulin and insulin analogues (Kazda et al., 2010). Insulin detemir has also been tested for mitogenic potency *in vitro* by the MAH (data are only submitted as preliminary data in the response document) and others (Weinstein et al., 2009). While Weinstein et al. (2009) showed slightly higher potencies of insulin detemir as compared to insulin in several cell lines (HCT-116, PC-3 and MCF-7 cancer cells), the MAH only observed lower potencies of insulin detemir as compared to insulin in a similar (MCF-7) and several different cell lines (Colo205, L6hIR and HMEC). The MAH is requested to submit the final study report has not been submitted. Following up to 26 weeks of treatment, insulin detemir was found to stimulate rat mammary gland cell proliferation *in vivo* to the same extent as human insulin. Hence, the available *in vitro* and *in vivo* non-clinical data suggest that the mitogenic potential of levemir is similar to that of native human insulin.

In carcinogenicity studies conducted with liraglutide, C-cell tumours were observed in mice and rats. A NOAEL value for these findings was established in mice at 0.2 mg liraglutide/kg/day, which results in plasma exposure levels similar to what is obtained in the clinic. A NOAEL value was not established in rats. A number of exploratory studies have been conducted in order to evaluate the mechanism behind carcinogenic effect of liraglutide on rodent C-cells. The relevance for humans is likely to be low but cannot be completely excluded. Other types of tumours were also observed in the carcinogenicity studies especially in female animals. However, the relevance of these tumour findings for human safety was considered limited to due the lack of an apparent dose-response relationship, sufficient safety margins and/or the experimental conditions. Both insulin and GLP-1 receptors are known to cause cell proliferation upon stimulation. Based on the current understanding of the molecular mechanisms of insulin and GLP-1 action, these hormones and their analogues activate different intracellular signalling pathways. Additive and synergic interactions are therefore not considered unlikely. However, the proliferative effects of these pathways seem to be limited to specific types of cells. Hence, insulin and GLP-1 including their analogues are unlikely to be general growth promoters.

Both insulin and GLP-1 receptors are known to cause cell proliferation upon stimulation. Based on the current understanding of the molecular mechanisms of insulin and GLP-1 action, these hormones and their analogues activate different intracellular signalling pathways. Additive and synergic interactions are therefore not considered unlikely. However, the proliferative effects of these pathways seem to be limited to specific types of cells. Hence, insulin and GLP-1 including their analogues are unlikely to be general growth promoters. On the contrary, it is expected that a potential proliferative response due to combination treatments with liraglutide and insulin detemir would depend on the responsiveness of the different cell types to both pathways. The present data indicate a clear distinction in the cell types responsive to either insulin or GLP-1 receptor activation in terms of cell proliferation and tumour formation. Furthermore, the MAH has studied the combined effect of insulin detemir and liraglutide on cell growth in a colon cancer cell line (only preliminary data were submitted by the MAH). These

preliminary data showed that increasing concentrations of liraglutide had no apparent influence on the concentration-response relationship of insulin detemir.

Overall, the weight of evidence for an additive or synergic tumour promotion due to combination treatments with metformin, insulin detemir and liraglutide is currently considered sparse from a non-clinical perspective and the potential risk is presently only theoretical.

Regarding the clinical data, MAH referred to the well-known association of type 2 diabetes and obesity with certain types of cancer. However, there are controversial publications from several predominantly epidemiological studies on the association between insulin, in particular insulin glargin, and cancer (Yang, Diabetes 2010, Hemkens, Diabetologia 2009, Jonasson, Diabetologia 2009, Colhoun, Diabetologia 2009, Rosenstock, Diabetologia 2009). The MAH also referred to an individual patient data meta-analysis of randomised trials sponsored by the MAH in 8693 patients (Dejgaard, Diabetologia 2009) where patients with insulin detemir had a lower or similar occurrence of cancer compared to patients treated with NPH insulin or insulin glargine, respectively. However, the trials were of limited duration, without post trial follow-up and not designed to assess the risk of cancer.

Accordingly, it is self-evident that final conclusions on a potential risk of detemir and liraglutide cannot be drawn from study NN2211-1842.

According to the CHMP, the signal of a tumour promoting risk is not as strong as to advice against updating the Victoza SmPC with the results of study NN2211-1842. It is, however, considered to important to follow up on this potential concern.

Without large randomised long term studies with cancer endpoints the issue of a potential growth promoting effect of the combination of insulin detemir and liraglutide cannot be answered. Based on the overall evidence currently available, however, the signal of a potential tumour promoting effect seems not as strong as to advise against the use of this combination treatment. In this respect the devastating effects of insufficiently controlled diabetes should also be weighed against this potential risk. The Pharmacovigilance measures proposed by the MAH are supported by the CHMP, and have been implemented in the RMP.

Pancreas related adverse events

Pancreas related adverse events were to be reported as MESIs to establish if there were indications of pancreatitis. The pancreas related adverse events reported during both run-in, main and extension period are presented in Table 20. The overall proportion of subjects reporting pancreas related adverse events was higher for the detemir+lira group compared to the lira-control group and non-randomised liraglutide group, 11.0% vs. 8.8% and 7.8%, respectively.

The most commonly reported pancreas related adverse events were increased lipase, reported by similar proportions of subjects within treatment groups and at 9.8%, 7.5% and 7.4% of subjects treated with insulin detemir + liraglutide 1.8 mg + metformin, liraglutide 1.8 mg + metformin and nonrandomised liraglutide 1.8 mg + metformin, respectively.

Four (4) cases of pancreatitis were reported by four subjects during the trial period. One subject with acute pancreatitis withdrew early. One (1) case of acute pancreatitis and one (1) case of chronic pancreatitis were diagnosed in the lira-control group, whereas one case of unspecified pancreatitis was diagnosed in the non-randomised liraglutide group.

Table 20: Pancreas related treatment emergent adverse event by System Organ Class and Preferred Term – Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early Withdrawals		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24			166		
Intensified	17						7			24					
All Adverse Events	14	(8.8)	15	18	(11.0)	18	39	(7.8)	42	2	(8.3)	2	5	(3.0)	6
Investigations	12	(7.5)	13	16	(9.8)	16	38	(7.6)	41	2	(8.3)	2	4	(2.4)	5
Lipase Increased	12	(7.5)	13	16	(9.8)	16	37	(7.4)	38	2	(8.3)	2	4	(2.4)	5
Blood Amylase Increased							3	(0.6)	3						
Gastrointestinal disorders	2	(1.3)	2	1	(0.6)	1	1	(0.2)	1				1	(0.6)	1
Pancreatic Disorder				1	(0.6)	1									
Pancreatitis							1	(0.2)	1						
Pancreatitis Acute	1	(0.6)	1										1	(0.6)	1
Pancreatitis Chronic	1	(0.6)	1												
Metabolism and nutrition disorders				1	(0.6)	1									
Hyperlipasaemia				1	(0.6)	1									

All subjects also received metformin
AEs of intensified subjects are tabulated in initial treatment group if the AE occurs before intensification. If the AE increases in severity after intensification it will be tabulated in both treatment groups
N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

Thyroid related adverse events

The overall proportion of subjects reporting thyroid related adverse events was 1.2%, 2.5% and 4.2% of subjects reporting an event in the detemir+lira group, lira-control group and the non-randomised liraglutide 1.8 mg + metformin treatment group, respectively. The most frequently reported thyroid related adverse event in all treatment groups was increased calcitonin, which was reported by single or few subjects in each treatment group. For the entire trial period, including follow-up information on adverse events reported in the 26-week main trial period, 3 thyroid neoplasms were reported (all in the non-randomised liraglutide 1.8 mg + metformin treatment group). No malignancy was suspected in any of these cases.

Cardiovascular safety

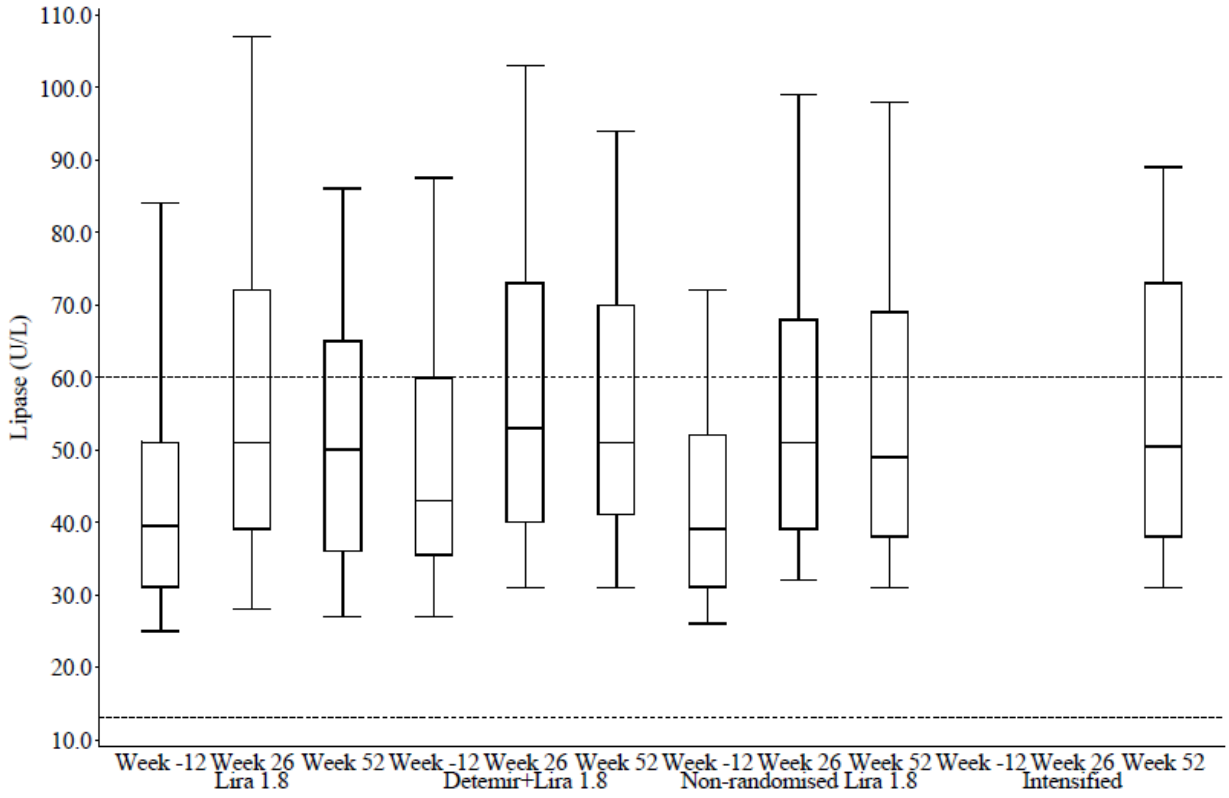
In line with previous experience from liraglutide trials and as reported in the original MAA, a slight increase in pulse was observed across treatment groups in all treatment groups during the run-in period. There was no difference seen between treatment groups.

Laboratory findings

The most common clinical laboratory adverse event in all treatment groups were increased lipase, reported by 16.0%, 10.1% and 11.0% for subjects in the detemir+lira group, lira-control group and the non-randomised liraglutide 1.8 mg + metformin group, respectively. Fluctuations in lipase values over time were observed for all subjects, with no apparent or consistent trends. A total of 124 subjects reported lipase values above 2x UNR in the main period of the trial (15.1%). Of these, 23 subjects had lipase values above 2x UNR at run-in. The increase in lipase did not appear to be associated with an increased reporting of gastrointestinal adverse events. One of the clinical laboratory adverse events was serious: increased lipase, reported by a subject treated with liraglutide 1.8 mg + metformin, and classified as severe. The subject recovered, without change in dose. It was clarified by the MAH that this difference in increased lipase was evident also before patients were randomised to study treatment. Serum lipase did not seem to increase over time in any of the treatment groups and most importantly, in study NN2211-1842 elevated serum lipase was not associated with increases in amylase or the observed events of pancreatitis.

In Figure 4, box plots are shown of lipase levels (U/L) at run-in, randomisation and end of study (Week 52) for all treatment groups.

Figure 4: Box plot of Run-In, Week 26 and 52 for Lipase (U/L) (LOCF) -SAS



All subjects also received metformin
Values outside axes ranges are all included in calculations
Box plot: Median (centre line), 25 and 75 percentiles (box),
10 and 90 percentiles (top and bottom)
Normal range: (13-60 U/L)

Overall, the clinical laboratory evaluations observed in the trial are in line with those reported in the original MAA.

Immunological events

Between Week 0 (randomisation) and Weeks 52 and 53, only single subjects tested positive for liraglutide antibodies. No treatment group difference in terms of numbers of subjects being positive over time was apparent. At Week 53, where only subjects who were off drug between Weeks 52 and 53 were included, 4 (3.7%), 2 (2.1%) and 15 (4.0%) subjects were positive for liraglutide antibodies in the insulin detemir + liraglutide 1.8 mg + metformin, liraglutide 1.8 mg + metformin and non-randomised liraglutide 1.8 mg + metformin treatment groups, respectively. All but one of these subjects had antibodies exhibiting cross-reactivity, whereas 7 subjects had antibodies demonstrating neutralising effects (1 subject treated with insulin detemir and 6 subjects treated with non-randomised liraglutide 1.8 mg + metformin).

Overall, levels of antibodies specific to insulin detemir remained low during the trial (mean 1.68 %B/T at Week 0 and mean 4.30 %B/T at Week 53 for subjects off drug between Weeks 52 and 53). A slight increase was observed from Week 0 (randomisation) to Week 53 (subjects off drug between Weeks 52 and 53) in antibodies with cross-reacting effect (mean -0.08 %B/T at Week 0 and mean 11.74 %B/T at Week 53).

Post-marketing reports of ketoacidosis

Since the PSUR submission in August 2010, a few spontaneous case reports of diabetic ketoacidosis, due to switch from insulin to Victoza in insulin dependent patients, were identified during routine safety surveillance of Victoza. Following the Japanese launch of Victoza, a cluster of cases was identified in Japan. Two of the cases had a fatal outcome. The product label in Japan was updated immediately following these incidences. The MAH proposed to update the Victoza SmPC to ensure correct use of the product and to prevent this inappropriate and off-label use.

A total of 334 cases of hyperglycaemia have been reported by the MAH. Of these cases, 26 were reported as serious adverse events and 308 as non-serious adverse events. Information on either current concomitant use of insulin (n=37/334) or switch from insulin (n=28/334) was available in 65 cases (50 non-serious cases; 15 serious cases).

From the total of 26 serious cases, 2 cases were confirmed type 1 diabetes mellitus patients (cases 292059; 312067). A total of 16 cases were reported as type 2 diabetes mellitus. From these cases, cases 309592 and 314183 were later suspected of having type 1 diabetes mellitus and case 314183 also was reported as having a positive anti-GAD antibody test; case 306877 was later diagnosed with Type 1 diabetes.

A total of 8 cases were reported as either 'drug used for unknown indication' or 'diabetes mellitus' without specification of subtype of disease. Among the 308 cases reported as non-serious, information on insulin treatment was available in 50 cases; 15 cases had information confirming a switch from an insulin-containing regimen, 35 cases had information confirming concomitant use of insulin.

It is not unusual for diabetic patients to experience bouts of hyperglycaemia even when they are on adequate therapy as glycaemic control depends on several factors apart from the therapy. This is acceptable as long as the hyperglycaemic episodes are transient and not serious. The non serious cases belong to that category.

In the complete data set of 334 hyperglycaemia cases, information confirming a switch from an insulin-containing regimen was available in 28/333 (8.4%). There was no pattern in the type of insulin-containing regimen to be switched from, as both basal-bolus regimens and premix regimens were reported. Of the 10 cases reported as diabetic ketoacidosis or ketoacidosis, 9 occurred after discontinuation of an insulin-containing regimen.

Duration of treatment of Victoza in the 26 serious cases ranged from 1 day to 175 days with a median of 16.5 days.

Upon identification of the Japanese cases, the MAH initiated actions to ensure appropriate use of the product. These actions are all described in the revised Risk Management Plan submitted with this application (please refer to the RMP section below).

Based on the described cases of hyperglycaemia the MAH proposed to amend section 4.4 of the SmPC and section 2 of the Package Leaflet (refer to section Changes to the SmPC, Annex II, Labelling and Package below).

1.2.8. Discussion on clinical safety

In study NN2211-1842, the mean duration of liraglutide treatment was 411 days for subjects in the detemir+lira group and 369 days for subjects in the lira-control group. The mean duration of insulin detemir treatment was about 326 days and with a total subject exposure time of 145 years for subjects in the detemir+lira group.

The overall pattern and frequencies of the most common adverse events in study NN2211-1842 when insulin detemir was added to the combination of liraglutide 1.8mg + metfomin was similar to the overall safety profile observed for liraglutide therapy + metformin therapy. The overall safety profile was further confirmed by week 52 safety data submitted by the MAH during the evaluation.

The AE-profile was initially only presented for AEs occurring in >5% of patients. Following a request from the CHMP, tables presenting TEAES with incidences >1% of subjects were provided by the MAH during the evaluation. No new safety concerns, besides the earlier mentioned malignancies, were identified.

Several adverse events were pre-specified as medical events of special interest (MESIs) most of them originating from the original MAA for liraglutide: pancreas related events, thyroid related events, injection site reactions and neoplasms. A potential signal of an increased lipase was noticed in 11% in the insulin detemir + liraglutide group compared to the other groups (3.4% and 3.8%). There was even a higher percentage of patients with increased lipase who were not specified as "pancreas related" lipase increases, with 16.0% subjects in the detemir+lira group, 10.1% in the lira-control group, and 11.0% in the non-randomised group. It was clarified that the difference between treatment groups was evident also before patients were randomised to study treatment. Serum lipase did not seem to increase over time in any of the treatment groups and most importantly, in study NN2211-1842 elevated serum lipase was not associated with increases in amylase or the observed events of pancreatitis.

Also of note is the frequency of neoplasms reported during study NN 2211-1842. During the main study period (26W) 0%, 0.6% and 2.0% were observed in the detemir+lira group, lira-control group and the non-randomised group, respectively. 52 Weeks safety data were submitted by the MAH during the evaluation in which it became apparent that 7 new cases (4.3%, 6 of them were malignant) of neoplasms were identified in the detemir+lira group during the 26 Week extension period of which one malignant case turned out to have a wrong date of onset (event occurred before administration of insulin detemir). No additional neoplasms were identified in the liraglutide-control group whereas two neoplasms (2.4%), of which one malignant, were observed in the non-randomised liraglutide+metformin group. There was no apparent clustering in the types of neoplasm seen in any of the detemir+liraglutide+metformin group. The number of malignant neoplasms was 5 in the triple combination arm. In the randomised lira-control group there was one malignant event. Whereas in the non-randomised lira+met arm; there were 5 malignant events in 4 patients. The percentage of malignant events was thus higher in the triple combination arm (5/163; 3.1%) compared to the pooled liraglutide + metformin arms (5/658; 0.8%). The MAH addressed this safety concern by providing non-clinical and clinical information, by conducting further statistical analyses and by providing narratives of all neoplasm cases. The majority of the malignant cases seems confounded by strong risk factors and contributing factors for cancer. None of the conducted post-hoc statistical analyses supported the concern regarding a growth promoting effect of the triple combination treatment. Based on the non-clinical data, the weight of evidence for an additive or synergic tumour promotion due to combination treatments with metformin, insulin detemir and liraglutide is currently considered sparse and inconclusive. Regarding the clinical data, the MAH referred to the well-known association of type 2 diabetes and obesity with certain types of cancer. With respect to the association between insulin, in particular insulin glargin (Lantus) there are controversial data and further data of ongoing observational studies are awaited. In summary, final conclusions on a potential risk of detemir and liraglutide cannot be drawn from the current study.

There were no major hypoglycaemic events during the main period. The rate of minor hypoglycaemic episodes was low, but as expected the highest rate for the detemir+lira group: 0.228, 0.034 and 0.115 events per subject years for patients in the detemir+lira group, lira-control group and the non-randomised liraglutide 1.8 mg+metformin, respectively. This difference in minor hypoglycaemic

episodes reported between the two randomised treatment groups was statistically significant (p=0.0011).

Conclusions on clinical safety

Overall, based on the safety data from this 52 Week study, the overall safety profile observed with insulin detemir in combination with liraglutide is comparable to what is already known for liraglutide and insulin detemir separately. However, more neoplasms were noted in the metformin + liraglutide + detemir group but the data are inconclusive. The MAH has updated their RMP with further pharmacovigilance activities to address this safety concern. This was considered acceptable by the CHMP.

1.2.9. Risk Management Plan

As part of this grouping of two type II variations, the MAH submitted an update of the Risk Management Plan (RMP) (version 13, dated 22 September 2011).

Safety Specification

Clinical safety concerns

Post Authorisation Experience

Newly Identified Safety Concerns

Safety concern	**Hyperglycemia due to discontinuation of insulin**
Details	Spontaneous reports of diabetic ketoacidosis due to discontinuation of insulin in insulin dependent patients were identified during routine safety surveillance of Victoza. Victoza was started in these patients subsequent to insulin discontinuation. Following the Japanese launch of Victoza, a cluster of cases was identified from Japan. Two of the cases had a fatal outcome. The product label in Japan was updated immediately following these incidences. Victoza is the first product of its class (GLP-1 analogue) on the market in Japan, which most likely contributed to the observed cluster of cases as other region have not had similar rates of discontinuation of insulin Based on these findings, the MAH decided to include hyperglycaemia due to discontinuation of insulin as an identified risk in the RMP.
Source	Spontaneous reports
Implications for product literature	CCDS and label update
New studies proposed in the pharmacovigilance plan	No
New risk minimisation actions proposed	CCDS update, label update and follow-up questions

Adverse Events/Adverse Reactions

Important identified risks

Hyperglycaemia due to discontinuation of insulin has been added as an important identified risks:

During routine post-marketing safety surveillance of spontaneous reports, the MAH identified reports containing events related to hyperglycaemia due to discontinuation of insulin in insulin-dependent patients. Victoza was started in these patients subsequent to insulin discontinuation. Hyperglycaemia is a known risk in patients who are dependent on insulin to maintain blood glucose homeostasis. When these individual discontinue insulin treatment they develop severe hyperglycaemia, which may lead to diabetic ketoacidosis or hyperglycaemic coma. The risk of hyperglycaemia is not related to Victoza, but is a consequence of the inappropriate discontinuation of insulin therapy. Therefore, the MAH decided to update the CCDS, 'hyperglycaemia due to discontinuation of insulin' was included as an identified risk in order to closely monitor these reports and follow-up questions have been developed.

Identified risk	**Hyperglycemia due to discontinuation of insulin***
Seriousness/outcomes	Spontaneous 28 reports
Severity and nature of risk	Severe
Frequency	Spontaneous:28 reports 0.12 events/PYE∗1000
Background incidence/prevalence	N/a
Risk groups or risk factors	All patients with diabetes dependent on insulin Discontinuation of insulin, in patients dependent on insulin, may lead to hyperglycaemia and diabetic ketoacidosis
Potential mechanisms	When patients dependent on insulin discontinue insulin treatment they develop severe hyperglycaemia
Preventability	Through the education of HCP and patients about the importance of maintaining insulin treatment in insulin-dependent patients
Potential public health impact of safety concern	Diabetic ketoacidosis is potentially lethal
Evidence source	Spontaneous reports and cumulative sales up to 12 Oct 2010

*Narrow PTs from the MedDRA SMQ Hyperglycaemia/new onset diabetes mellitus (SMQ# 20000041 version 13.0)

Pharmacovigilance Plan

Routine Pharmacovigilance Practices

Hyperglycaemia due to discontinuation of insulin has been added as an identified risk which will be monitored by routine pharmacovigilance.

Action Plan for Safety Concerns

Important identified risks	Proposed action	Description
Hyperglycaemia due to discontinuation of insulin	Action(s) proposed	Routine pharmacovigilance activities, e.g. continued and ongoing analyses of safety data from spontaneous sources and planned clinical trials. Targeted safety surveillance will be applied to all reports of hyperglycaemia related adverse events by introducing a questionnaire requesting follow-up information for single events, with particular information on discontinuation of insulin
	PIL and SPC	Section 4.4 Special warnings and special precautions for use: - Victoza is not a substitute for insulin
	Detail further measures	None.
	Milestones	Aligned with the post-approval periodic safety update reports (PSURs).

Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Identified Risks		
Hypoglycaemia	• Routine and targeted pharmacovigilance • Analyses of ongoing and planned clinical trials	Labelling – SmPC: • Sec. 4.2 Posology and method of administration. o Patients receiving Victoza® in combination with a sulphonylurea may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by a reduction in the dose of sulphonylurea • Sec. 4.4 Special warnings and precautions for use. o Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis • Sec. 4.8 Undesirable effects o Most episodes of confirmed hypoglycaemia in clinical studies were minor. No episodes of major hypoglycaemia were observed in the study with Victoza® used as monotherapy. Major hypoglycaemia may occur when Victoza® is combined with a sulphonylurea (uncommon) or oral anti-diabetics other than sulphonylureas (rare).

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Gastrointestinal adverse events	• Routine pharmacovigilance • Analyses of ongoing and planned clinical trials	Labelling – SmPC: • Sec. 4.2 Posology and method of administration o Dose-titration algorithm described to mitigate gastro-intestinal adverse events • Sec. 4.8 Undesirable effects o When combining Victoza® with metformin. 20.7% of patients reported at least one episode of nausea, and 12.6% of patients reported at least one episode of diarrhoea. When combining Victoza® with a sulphonylurea. 9.1% of patients reported at least one episode of nausea and 7.9% of patients reported at least one episode of diarrhoea.
Hyperglycaemia due to discontinuation of insulin	• Routine and targeted pharmacovigilance	Labelling – SmPC • Sec 4.4 Special warnings and precautions for use o Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. o Victoza® is not a substitute for insulin
Potential Risks		
Altered renal function	• Routine and targeted pharmacovigilance • Analyses of ongoing and planned clinical trials	Labelling – SmPC • Sec. 4.4 Special warnings and precautions for use: Signs and symptoms of dehydration, including altered renal function have been reported in patients treated with Victoza®. Patients treated with Victoza® should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.
Medullary thyroid cancer	• Routine and targeted pharmacovigilance • Database studies (NN2211-3784 and NN2211-3880) • Medullary thyroid carcinoma registry (MTC- 22341) • Analyses of ongoing and planned clinical trials	Labelling– SmPC • Sec. 4.4 Special warnings and precautions for use o Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in clinical trials in particular in patients with pre-existing thyroid disease • Sec 4.8 Undesirable effects o The overall rates of thyroid adverse events in all intermediate and long-term trials are 33.5. 30.0 and 21.7 events per 1000 subject years of exposure for total liraglutide, placebo and total comparators; 5.4. 2.1 and 1.2 events, respectively concern serious thyroid adverse events. Thyroid neoplasms, increased blood calcitonin and goiters were the most frequent thyroid adverse events. The rates per 1000 subject years of exposure were 6.8. 10.9 and 5.4 of liraglutide treated patients in comparison with 6.4. 10.7 and 2.1 of placebo treated and 2.4. 6.0 and 1.8 of total comparator treated patients respectively.

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
		Cardiovascular Outcome Trial (EX2211-3748. LEADER™) 2 non-clinical studies (NN210145 and NN209306. See Table 59)
Neoplasm	• Routine and targeted pharmacovigilance • Database studies (NN2211-3784 and NN2211-3880) • Analyses of ongoing and planned clinical trials	Cardiovascular Outcome Trial (EX2211-3748. LEADER™)
Cardiovascular disorders	• Routine pharmacovigilance • Analyses of ongoing and planned clinical trials including a cardiovascular outcome study • Database studies (NN2211-3784 and NN2211-3880)	Labelling – SmPC • Sec. 4.4 Special warnings and precautions for use o There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II. There is no experience in patients with congestive heart failure NYHA class III-IV. Cardiovascular Outcome Trial (EX2211-3748. LEADER™)
Late-stage microvascular complication of the eye	• Routine pharmacovigilance • Analyses of ongoing and planned clinical trials	Cardiovascular Outcome Trial (EX2211-3748. LEADER™)
Immunogenicity (anti-liraglutide antibody formation, allergic reactions and injection site reactions)	• Routine and targeted pharmacovigilance • Analyses of ongoing and planned clinical trials	Labelling – SmPC • Sec. 4.8 Undesirable effects o Anti-liraglutide antibody formation o Angioedema o Injection site reactions o Urticaria (pending approval for SmPC) Cardiovascular Outcome Trial (EX2211-3748. LEADER™)
Pancreatitis	• Routine and targeted pharmacovigilance • Database studies (NN2211-3784 and NN2211-3880) • Analyses of ongoing and planned clinical trials • 1 non-clinical study LoSi100801	Labelling – SmPC • Sec. 4.4 Special warnings and precautions for use o Use of GLP-1 analogues has been associated with the risk of pancreatitis. There have been few reported events of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected. Victoza® and other potentially suspect medicinal products should be discontinued. • Sec 4.8 Undesirable effects o Few cases (<0.2%) of acute pancreatitis have been reported during long-term clinical trials with Victoza®.

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
		Cardiovascular Outcome Trial (EX2211-3748. LEADER™)
Malignant neoplasms following combination treatment with insulin detemir + liraglutide + metformin	• Single case reporting including targeted follow-up questions • Aggregated periodic reporting- these cases will be described and evaluated in dedicated sections within the PSURs and DSURs • Non-clinical study on the *in vitro* mitogenicity in various cell lines • Literature search on the mitogenic potency of insulin and insulin analogues	Not applicable
	• Non-clinical study on the combined effect of insulin detemir and liraglutide on cell growth • Pharmacoepidemiological study using GPRD • A feasibility report of conducting additional analysis within the cardiovascular outcome trial (EX2211-3748, LEADER™) to look at the incidence of tumours with the combination of liraglutide and insulin detemir. • Statistical analyses plan for the on-going cardiovascular outcome trial (EX2211-3748, LEAD-ER™) will be provided	

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Missing Information		
Abuse due to weight lowering potential	• Routine pharmacovigilance	Available as prescription only
Children and adolescents	• Clinical trial (NN2211-1800) • Routine pharmacovigilance	Labelling – SmPC • Sec. 4.2 Posology and method of administration o Victoza® is not recommended for use in children below 18 years of age due to lack of data on its safety and efficacy
Overdose	• Routine pharmacovigilance	Labelling – SmPC • Sec. 4.9 Overdose o In a clinical study of Victoza®, one patient with type 2 diabetes experienced a single overdose of 17.4 mg subcutaneous (10 times the maximal recommended maintenance dose of 1.8 mg). Effects of the overdose included severe nausea and vomiting, but not hypoglycaemia. The patient recovered without complications. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms
Pregnant and lactating women	• Routine pharmacovigilance	Labelling – SmPC • Sec. 4.6 Pregnancy and lactation o Pregnancy: There are no adequate data from the use of Victoza® in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Victoza® should not be used during pregnancy, and the use of insulin is recommended instead. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Victoza® should be discontinued. o Lactation: It is not known whether liraglutide is excreted in human milk. Animal studies have shown that the transfer of liraglutide and metabolites of close structural relationship into milk is low. Non-clinical studies have shown a treatment-related reduction of neonatal growth in suckling rat pups. Because of lack of experience. Victoza® should not be used during breast-feeding.
Potential interaction with warfarin	• Routine pharmacovigilance	Labelling – SmPC • Sec. 4.5 Interaction with other medicinal products and other forms of interaction o No interaction study has been performed. A clinically relevant interaction with active substances with poor solubility or with narrow therapeutic index such as warfarin cannot be excluded. Upon initiation of liraglutide treatment in patients on warfarin or other coumarin derivatives more frequent monitoring of INR is recommended.

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Congestive heart failure NYHA III-IV	• Routine pharmacovigilance	Labelling – SmPC • Sec. 4.4 Special warnings and precautions for use o There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II. There is no experience in patients with congestive heart failure NYHA class III-IV. Cardiovascular Outcome Trial (EX2211-3748. LEADER™)
Renal and hepatic impairment/endstage renal failure	• Routine pharmacovigilance	Labelling – SmPC • Sec. 4.2. Posology and metod of administration: *Renal impairment*: Not recommended for use in patients with moderate and severe renal impairment including patients with end-stage renal disease. *Hepatic impairment:* The therapeutic experience in patients with all degree of hepatic impairment is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment. Cardiovascular Outcome Trial (EX2211-3748. LEADER™)
Off-label use	• Routine pharmacovigilance	Full SmPC.

The CHMP, having considered the data submitted in RMP version 13, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Final study report on the in vitro mitogenicity in various cell lines	31 December 2011
A literature search on the mitogenic potency of insulin and insulin analogues	31 December 2011
Final study report on the combined effect of insulin detemir and liraglutide on cell	31 December 2011
A feasibility report of conducting additional analysis within the cardiovascular outcome trial (EX2211-3748, LEADER) to look at the incidence of tumours with the combination of liraglutide and insulin detemir	31 December 2011
Statistical analysis plan for the ongoing cardiovascular outcome trial (EX2211-3748, LEADER) will be provided for review	31 December 2012
Draft protocol addendum for the planned pharmaco-epidemiology study using GRPD	31 December 2011

No additional risk minimisation activities were required beyond those included in the product information.

1.2.10. Changes to the SmPC, Annex II, Labelling and Package Leaflet

Following the assessment of this grouping of two type II variations, the CHMP endorsed the following changes to the SmPC and to the Package Leaflet (underlined = new text, strikethrough = deleted text):

Section 4.4 Special warnings and precautions for use of the SmPC

Victoza is not a substitute for insulin.

The addition of liraglutide in patients already treated with insulin has not been evaluated and is therefore not recommended.

Section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC

Insulin
No pharmacokinetic or pharmacodynamic interactions were observed between liraglutide and insulin detemir when administering a single dose of insulin detemir 0.5 U/kg with liraglutide 1.8 mg at steady state in patients with type 2 diabetes.

Section 5.1 Pharmacodynamic properties of the SmPC

In a 52 week clinical trial, the addition of insulin detemir to Victoza® 1.8 mg and metformin in patients not achieving glycemic targets on Victoza® and metformin alone, resulted in a HbA1c decrease from baseline of 0.54%, compared to 0.20% in the Victoza® 1.8 mg and metformin control group. Weight loss was sustained. There was a small increase in the rate of minor hypoglycaemic episodes (0.23 versus 0.03 events per subject years. The addition of liraglutide in patients already treated with insulin has not been evaluated (see section 4.4).

Section 2 Before you use Victoza of the Package Leaflet

Victoza should not be used if you have type 1 diabetes or diabetic ketoacidosis. Victoza is not an insulin. Victoza should not be used in children and adolescents under 18 years.

In particular, tell your doctor, nurse or pharmacist if you are using medicines for diabetes containing any of the following active substances:
- insulin. Victoza is not recommended if you are already using insulin.

In addition the MAH has taken the opportunity to align the Annexes with version 7.3.1 of the QRD template, to delete the DDPS version number and to update the RMP version number from Annex IIB. Minor editorial changes have been made throughout the Annexes. Finally in section 6 of the Package Leaflet , the pictures for the instructions of using Victoza have been changed so that the fingers in the pictures are now white instead of yellow.

The CHMP agreed with the changes to the Annexes requested by the MAH listed above.

2. Benefit Risk Balance

Benefits

Initially, the MAH claimed an extension of the indication for Victoza: "In combination with basal insulin in patients not achieving adequate glycaemic control with Victoza and metformin". This was not considered acceptable by the CHMP, as this is an indication for insulin detemir and not for Victoza. To get an extension of indication for Victoza, the added value of adding Victoza to insulin detemir + metformin should be demonstrated in terms of efficacy and safety. The design of study NN2211-1842 only gives information about the efficacy and safety of insulin detemir when added to metformin + liraglutide. The shortcomings of study NN2211-1842 were acknowledged by the MAH who proposed to include instead only some efficacy and safety data regarding study NN2211-1842 in section 5.1 of the SmPC.

The MAH submitted two clinical trials: one PK/PD trial (study NN2211-3673)and one clinical efficacy and safety study (study NN2211-1842).

During the PK/PD study (study NN2211-3673), no pharmacokinetic interaction between insulin and liraglutide was observed. According to the predefined *no effect* boundary of [0.8, 1.25], liraglutide at steady state did not affect the pharmacokinetic endpoints (AUC, C_{max}) of insulin detemir and vice versa. No pharmacodynamic interaction was observed; the treatments had an additive effect. The sum of the mean AUC_{GIR} for liraglutide and insulin detemir given individually was similar to that obtained when the two were given in combination.

In the clinical efficacy and safety trial NN221-1842 patients included were a relatively healthy subgroup of type 2 DM patients. Furthermore, the trial design was open-label. The study duration was 52 weeks, and the number of patients participating in the study was limited (total study population 323 patients). Patients inadequately controlled by Metformin (≥1500 mg daily) or Metformin + low dose SU (≤ half maximum dose) were switched to Metformin (same dose) + Liraglutide 1.8 mg daily. Subjects not adequately controlled after 12 weeks were randomised to receive insulin detemir as add-on to Metformin + Liraglutide or continued on Metformin + Liraglutide. Addition of insulin to liraglutide + metformin demonstrated a favourable, clinically relevant effect on the blood glucose control in terms of HbA1c reduction. The change from baseline in HbA1c in the triple therapy group at week 26 was (LS mean changes) -0.51%, vs. +0.02% in the metformin + liraglutide group (difference -0.52 [CI: -0.68; -0.36]). The estimated proportions of subjects achieving HbA1c both <7% and ≤6.5% were significantly greater with insulin detemir + liraglutide 1.8 mg + metformin (44% and 19%) compared to liraglutide 1.8 mg + metformin (20% and 7%).

Improvements in other endpoints of glucose control were observed, including mean change in FPG and changes in post-prandial glucose levels. The glucose lowering effects were sustained during the extension period up to week 52.

After 52 weeks, a mean reduction in body weight was observed in all treatment groups. However, the reduction in body weight was less when insulin was added to the metformin + liraglutide treatment. The estimated mean reductions in body weight were 0.05 kg and 1.02 kg in the detemir+lira group and lira-control group, respectively, with an estimated mean difference (95% CI) between groups of 0.97 (0.04; 1.91), p=0.0416.

Risks

The overall pattern and frequencies of the most common adverse events in study NN2211-1842 corresponds to what was observed during the original MAA for liraglutide and insulin detemir, except for the frequency of nasopharyngitis which was considerably higher in the lira-control group vs. the other two treatment groups after 26 weeks as well as vs. the original dossier for liraglutide 1.8% (20.8% vs. 11.0-14.7% vs. 8.8%).

The most commonly reported adverse events during the 52-Week study (run-in, 26-week main and 26-week extension period) were nasopharyngitis, nausea and, diarrhoea reported by 20.2%, 18.4% and 17.8% in the detemir+lira group versus and 25.2%, 23.3% and 16.4% of subjects in the lira-control group. Thyroid related adverse events were reported in all treatment groups, with 1.2% and 2.5% of subjects reporting an event in the detemir+lira group and the lira-control group respectively.

The proportion of subjects reporting serious adverse events during the 52-Week trial period was 10.4% in the detemir+lira group, versus 6.9% in the lira-control group. Most of the serious adverse events were evaluated as unlikely related to trial product and no clustering of events was observed.

No major hypoglycaemic events were seen during the main period of the trial. The rate of minor hypoglycaemic episodes was higher in the detemir+lira group, compared with the lira-control group, with 0.228 and 0.034 events per subject years respectively. The estimated rate ratio (detemir+lira group/lira-control group) in minor hypoglycaemic episodes was 6.80 (2.14; 21.60), p=0.0011.

After submission of the safety data from the 26 weeks extension study it became apparent that the number of patients with a neoplasm was highest in the triple combination arm (insulin detemir + liraglutide + metformin). The number of malignant neoplasms was 6 in the triple combination arm, of which one, however, had a wrong date of onset (event occurred before administration of insulin detemir) which leaves 5 patients with malignant event. In the randomised liraglutide + metformin arm, there was 1 patient with a malignant neoplasm and in the non-randomised lira+met arm arm there were 5 malignant events in 4 patients. The percentage of malignant events was thus higher in the triple combination arm (5/163; 3.1%) compared to the pooled liraglutide + meformin arms (5/658; 0.8%).

The overall incidence of pancreas-related TEAEs was higher in the detemir+lira group (11.0%) when compared the randomised and non-randomised liraglutide + metformin groups (7.5% and 5.4%). The increased incidence was mainly related to increases in blood lipase.

Thyroid related AEs were comparable across treatment groups and was overall comparable to the frequency observed in the original MAA for Liraglutide. The most frequently reported thyroid related adverse event in all treatment groups was increased calcitonin, which was reported by single or few subjects in each treatment group.

Liraglutide and insulin detemir antibodies were observed, however, the duration of the study seems too short to determine the relevance of the observed antibodies for long term efficacy and safety.

Based on the original dossier cardiac events represent a possible concern for liraglutide and is included in the RMP for liraglutide as a potential risk. In addition, long-term follow up data on cardiac safety is being collected in the 5 year cardiovascular outcome study. Study NN2211-1842 did not show increased cardiac safety issues in the liraglutide + insulin detemir + metformin group compared to the liarglutide control group.

Benefit-Risk Balance

In clinical study NN2211-1842, the addition of insulin to patients insufficiently controlled with metformin and liraglutide demonstrated a favourable, clinically relevant effect on blood glucose control in terms of HbA1c reduction, including an increased proportion of patients achieving the clinically relevant goal of HbA1c < 7%. This is supported by the effect on FPG, and post-prandial glucose levels seen during the study. No unexpected effects occurred; an increased incidence of hypoglycaemia was observed, but not unexpectedly high and low in severity.

However, this study raised some major issues.

Firstly, this study design only gives information about the efficacy and safety of insulin detemir when added to metformin + liraglutide and not about the efficacy and safety of liraglutide added to insulin. Triple therapy might have an advantage over combination treatment with metformin and insulin alone in terms of lower insulin dosage, fewer hypoglycaemic episodes and less weight gain, while achieving the same level of glucose control. However, this was not studied in this trial and currently, literature to address this possible advantage is lacking. Thus, the combination cannot be accepted as a separate indication. However, information on the addition of insulin to liraglutide is considered relevant for daily practice and therefore information on this combination has been added in the relevant sections of the SmPC.

The excess incidence of malignant neoplasms in the triple combination arm (insulin detemir + liraglutide + metformin) is a major safety concern. Despite the fact that the neoplasms represent different locations and types/histology, a general tumour promoting effect cannot be excluded. The MAH addressed this issue by providing non-clinical and clinical information, by conducting further statistical analyses and by providing narratives of all neoplasm cases. The majority of the malignant cases seem confounded by strong risk factors and contributing factors for cancer. None of the conducted post-hoc statistical analyses supported the concern regarding a growth promoting effect of the triple combination treatment. Based on the non-clinical data, the weight of evidence for an additive or synergic tumour promotion due to combination treatments with metformin, insulin detemir and liraglutide is currently considered sparse and inconclusive. Regarding the clinical data, the MAH referred to the well-known association of type 2 diabetes and obesity with certain types of cancer. With respect to the association between insulin, in particular insulin glargin (Lantus) and cancer, the currently available data are controversial and further data from the ongoing observational studies are awaited. In summary, final conclusions on a potential increased risk of cancer with the combination of insulin detemir and liraglutide cannot be drawn from study NN2211-1842. This issue is addressed by the MAH in the RMP. Further data will be obtained both from observational data and data from the liraglutide randomised clinical CV outcome study.

Pancreatitis related events were reported, but the incidence was very low, allowing no conclusions. None of the 2 cases of pancreatitis occurred in the triple therapy group, but the overall incidence of pancreas-related TEAEs was higher in this group. The increased incidence was mainly related to increases in blood lipase. This was the first trial with regular lipase and amylase measurements. It is acknowledged that although serum lipase and amylase elevations may be diagnostic of pancreatitis (levels usually above three times the UNL) the prevalence in patients with type 2 diabetes mellitus is not well characterised. Already at run-in, patients had relatively high lipase levels and these levels did not seem to increase over time in any of the treatment groups. Most importantly, in study NN2211-1842 elevated serum lipase was not associated with increases in amylase or the observed events of pancreatitis. A placebo arm would have been necessary in order to get a clearer picture on the clinical relevance of increases of lipase levels.

Thyroid related AEs were comparable across treatment groups and was overall comparable to the frequency observed in the original MAA for Liraglutide. The most frequently reported thyroid related

adverse event in all treatment groups was increased calcitonin, which was reported by single or few subjects in each treatment group.

Liraglutide and insulin detemir antibodies were observed, however, the duration of the study seems too short to determine the relevance of the observed antibodies for long term efficacy and safety.

Altogether, combination therapy of metformin + liraglutide + basal insulin might be useful in a selective patient population for the treatment of diabetes mellitus type 2.

Conclusions on the Benefit-Risk Balance

The indication for the combination of liraglutide + metformin with basal insulin has not been accepted by the CHMP as information on the addition of liraglutide to insulin detemir + metformin is lacking. However, information on the addition of insulin detemir to liraglutide is considered relevant for daily practice and therefore information on this combination in the SmPC is considered acceptable in the relevant sections.

3. Conclusion

Victoza II/05/G was submitted as a group of variations consisting of two type II variations according to Article 7.2.(b) of Commission Regulation (EC) No 1234/2008.

Variation(s) requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

- Extension of indication for the treatment of type 2 diabetes in combination with basal insulin in patients not achieving adequate glycaemic control with Victoza and metformin alone: update to sections 4.1, 4.5, 4.8 and 5.1 of the SmPC and consequential changes to sections 1 and 2 of the Package Leaflet
- Update to section 4.4 of the SmPC to include a warning that Victoza is not a substitute for insulin and consequential changes to section 2 of the Package Leaflet, following post-marketing spontaneous reports of ketoacidosis in patients switching from insulin to Victoza. In addition the MAH has taken the opportunity to align the Annexes with version 7.3.1 of the QRD template and to delete the DDPS version number from Annex IIB. Minor editorial changes have been made throughout the Annexes. Finally in section 6 of the Package Leaflet, the pictures for the instructions of using Victoza have been changed so that the fingers in the pictures are now white instead of yellow.

Due to the major objections raised by the CHMP on the design of study NN2211-1842, the MAH did not pursue anymore an extension of indication for Victoza for the treatment of type 2 diabetes in combination with basal insulin in patients not achieving adequate glycaemic control with Victoza and metformin alone but instead proposed to update the Victoza SmPC with the results of study NN2211-1842.

On 22 September 2011 the CHMP considered this group of two type II variations:

- Update to sections 4.4, 4.5 and 5.1 of the SmPC and consequential changes to section 2 of the Package Leaflet based on the results of study NN2211-3673 (combination of insulin deternir +

Victoza pharmacology study) and study NN2211-1842 (phase III study investigating the efficacy and safety of adding insulin detemir to the combination Victoza + metformin).

- Update to section 4.4 of the SmPC to include a warning that Victoza is not a substitute for insulin and consequential changes to section 2 of the Package Leaflet, following post-marketing spontaneous reports of ketoacidosis in patients switching from insulin to Victoza. In addition the MAH has taken the opportunity to align the Annexes with version 7.3.1 of the QRD template, to delete the DDPS version number and to update the RMP version number from Annex IIB. Minor editorial changes have been made throughout the Annexes. Finally in section 6 of the Package Leaflet, the pictures for the instructions of using Victoza have been changed so that the fingers in the pictures are now white instead of yellow.

to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.