Assessment report

Levemir

insulin detemir

**Procedure No.:** EMEA/H/C/000528/II/0048

**Note**

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

1.1. Introduction

Levemir (insulin detemir) is an analogue of insulin human with a prolonged duration of effect.

On 01 June 2004 Levemir was granted a marketing authorisation for the following indication: Levemir as the basal component in a basal–bolus regimen for treatment of type 1 and type 2 diabetes. Later, in 2006, the Levemir label was extended to include combination with oral antidiabetic drugs (OADs) in type 2 diabetes (EMEA/H/C/528/II/0016).

The active substance in Levemir is insulin detemir.

This variation deals with the use of insulin detemir together with a glucagon-like peptide 1 (GLP-1) receptor agonist, liraglutide, for subjects with type 2 diabetes inadequately controlled on a treatment regimen of liraglutide in combination with metformin.

The variation submitted is the following:

<table>
<thead>
<tr>
<th>Variation(s) requested</th>
<th>Type</th>
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<tbody>
<tr>
<td>C.I.6.a</td>
<td>Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</td>
</tr>
<tr>
<td>II</td>
<td></td>
</tr>
</tbody>
</table>

Extension of indication for the use of Levemir as add-on therapy to liraglutide treatment affecting sections 4.2, 5.1 and 5.2 of SmPC. Package Leaflet has been updated accordingly. In addition, minor changes have been made throughout the Product Information.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/269/2010)

• Treatment of Type 1 Diabetes Mellitus
• Treatment of Type 2 Diabetes Mellitus

On the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

1.1.1. Clinical aspects

Although the mechanisms of action of insulin detemir and liraglutide are different, it is expected that the two drugs would complement each other in terms of efficacy.

Two trials were submitted in support of this variation; a confirmatory phase 3b clinical trial, NN2211-1842 (Trial 1842) with a 26-week treatment period and co-administration of insulin detemir and Liraglutide in subjects with type 2 diabetes and a phase 1 pharmacokinetics (PK) / pharmacodynamics (PD) trial, NN2211-3673 (Trial 3673), in which the PK and PD characteristics of insulin detemir, liraglutide and insulin detemir coadministered with liraglutide were investigated.
Trials and Data Included in the Clinical Overview

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

1.1.2. Pharmacokinetics

The clinical pharmacology trial NN2211-3673 (Trial 3673) 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 (Cmax) after administration of insulin detemir administered alone and when coadministered with liraglutide at a steady-state dose of 1.8 mg/day, the hypothesis being that the PK of insulin detemir is not substantially affected by co-administration of liraglutide.

Overview of Clinical Pharmacology, Trial 3673

1.1.2.1. Methods

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

Subjects were required to be naïve to insulin detemir and liraglutide and inadequately controlled by current treatment. 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.
Trial Design (Trial 3673)

- Analytical methods

A specific enzyme-linked immunosorbent assay was used to determine the serum insulin detemir concentrations. Liraglutide was determined by an enzyme-linked immunosorbent assay (ELISA) method. The bioanalytical and assay validation reports for liraglutide have been provided.

- Pharmacokinetic data analysis

The primary endpoints were the ratios between endpoints derived from single administrations of insulin detemir and co-administration of insulin detemir and liraglutide:

- $C_{\text{max}}$ of insulin detemir (single administration)/ $C_{\text{max}}$ of insulin detemir (co-administered with liraglutide)

- $\text{AUC}_{0-24\text{h}}$ of insulin detemir (single administration)/ $\text{AUC}_{0-24\text{h}}$ of insulin detemir (co-administered with liraglutide)

Secondary PK endpoints included the corresponding endpoints for liraglutide.

- Statistical analysis

The PK endpoints $C_{\text{max}}$ and $\text{AUC}_{0-24\text{h}}$ were log transformed and analysed separately in a linear mixed-effect model with treatment (with or without liraglutide) as fixed effect and subjects as random effect. The geometric mean treatment ratios were estimated and the 90% confidence intervals (CIs) constructed. The 90% CI was assessed relative to the $[0.8; 1.25]$ CI. If the constructed 90% CI was entirely encompassed within the $[0.8; 1.25]$ CI for both endpoints, it would be concluded that $C_{\text{max}}$ and $\text{AUC}_{0-24\text{h}}$ for insulin detemir were not substantially affected by co-administration of liraglutide in a steady-state dosing. The primary analysis was done both for the full analysis set (FAS) and for the completers (PP).
1.1.2.2. Absorption

- **Bioavailability**

The pharmacokinetics of insulin detemir is not influenced by the simultaneous presence of liraglutide and vice versa. It has been demonstrated, that a single dose of insulin detemir co-administered with steady-state dosing of liraglutide does not alter the pharmacokinetics of either of the two drugs in question. There is no reason to suspect altering of either of the two drugs pharmacokinetics with continuous co-administration of detemir and liraglutide.

1.1.2.3. CHMP overall conclusions on pharmacokinetics

No pharmacokinetic 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.

1.1.3. Pharmacodynamics

The glucose infusion rate (AUCGIR,0–24h) during insulin detemir administration, detemir administration, and co-administration of both drugs was determined in order to assess the glucose-lowering effect. For trial design and study design please see above.

1.1.3.1. Mechanism of action

**Detemir** is an insulin analogue and treatment with the compound has been associated with a lower risk of hypoglycaemia and less body weight gain compared with NPH insulin. Detemir exerts its effect through binding to and activation of the insulin receptor.

**Liraglutide** have been shown to elicit a glucose lowering effect – reducing fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) – increase insulin secretion, restore beta-cell sensitivity to glucose and delay gastric emptying. Importantly, during episodes of hypoglycaemia, liraglutide did not impair glucagon action or the general counter-regulatory response, and had no insulinotropic effect. Liraglutide exerts its effect through binding to and activation of the GLP-1 receptor.

1.1.3.2. Primary and Secondary pharmacology

1.1.3.2.1. Primary pharmacology

Continuous glucose infusion was provided to maintain blood glucose at a constant level of 5.5 mmol/L (100 mg/dL) ± 10%. The GIR during the clamp was used as a measure of the glucose-lowering effect of the administered drugs.

The following endpoints were derived both during single dose administrations of insulin detemir or liraglutide, and during coadministration of insulin detemir and liraglutide in the euglycaemic clamp settings:

- GIRmax maximum glucose infusion rate
- AUCGIR 0–24h area under the GIR curve from time 0 to 24 hours
- tGIRmax time to maximum glucose infusion rate

Plasma insulin, C-peptide and glucagon were measured during single dose administration of insulin detemir or liraglutide (steady-state) and co-administration of insulin detemir and liraglutide.
All analyses were based on ratios of endpoints measured during single administration of insulin detemir versus measurements made during co-administration of insulin detemir and liraglutide.

The smoothed pharmacodynamic GIR (glucose infusion rates) profiles of insulin detemir (0.5 U/kg), liraglutide (1.8 mg/day), and when insulin detemir and liraglutide is co-administrated are presented in Figure below.

![Mean Smoothed GIR Profiles](image)

**Mean Smoothed GIR Profiles**

Overall, the data show that AUC and SGIRmax are higher during co-administration of liraglutide and insulin detemir than when the drugs are given alone. The tSGIRmax estimated for the individual drugs given alone were very similar (12.2 h and 12.3 h) and was slightly later (12.8 h) when the drugs were co-administered.

1.1.3.2.2. Secondary pharmacology

The average C-peptide concentration over the 24-hour euglucaemic clamp procedure was higher with liraglutide at steady state (950.3 pmol/L) compared with insulin detemir alone (336.4 pmol/L) and compared with liraglutide co-administered with insulin detemir (791.9 pmol/L). The same pattern was found for $C_{\text{max}}$. The ratio analyses showed a significantly higher ratio of liraglutide vs. insulin detemir + liraglutide and a significantly lower ratio of insulin detemir vs. insulin detemir + liraglutide. The data reflect the ability of liraglutide to stimulate endogenous insulin secretion.

Glucagon secretion was lower during steady-state liraglutide dosing than during insulin detemir administration (both $C_{\text{av}(0-24h)}$ and $C_{\text{max}}$ was lower), and was even lower when liraglutide was co-administered with insulin detemir. The analyses showed that $C_{\text{av}(0-24h)}$ and $C_{\text{max}}$ were significantly higher when insulin detemir was administered alone than when co-administered with liraglutide; the values were also higher when liraglutide was administered alone compared to insulin detemir + liraglutide co-administration, but only significantly lower for $C_{\text{av}(0-24h)}$ only. The results are in line with previous observations showing the ability of liraglutide to lower the glucagon level in a glucose dependent manner.
1.1.3.2.3. CHMP overall conclusion on pharmacodynamics

No 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. Both treatments and the combination of the treatments were well tolerated.

1.1.4. Clinical efficacy

1.1.4.1. Main study

Study NN2211-1842:

A 26-week, randomised, open-label, two-armed, parallel-group, multicentre, multinational trial with a 26-week extension to evaluate the effect of insulin detemir in combination with liraglutide and metformin vs. liraglutide and metformin in subjects with type 2 diabetes. An open-label, non-randomised arm with subjects who achieved target glycaemic control after the run-in period was included to evaluate the long-term sustainability of glycaemic control and safety data.

The study was conducted in 202 centres in 9 countries: Belgium (2), Canada (7), France (19), Germany (37), Italy (18), the Netherlands (16), Spain (14), the United Kingdom (32) and the United States (57).

Trial period: 3rd of March 2009 – 19th of April 2010 (main period of 26 weeks).

1.1.4.2. Method

- Study Participants

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 that patients insufficiently controlled on metformin and low dose SU also were included. This sub-segment 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 was acceptable.

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

- **Trial design and Treatments**

Subjects with type 2 underwent screening, and if eligible, entered a 12-week run-in period with liraglutide (1.8 mg/day). When entering run-in, sulphonylurea treatment (if applicable) was discontinued, while treatment with metformin remained unchanged (same dose and dosing regimen). Treatment with liraglutide was initiated in 0.6 mg/day weekly increments to allow a final dose of 1.8 mg/day.

Subjects with an HbA1c greater than or equal to 7.0% after the run-in period were randomised in a 1:1 manner to intensification of treatment with insulin detemir added to the combination of liraglutide and metformin, or to continue with liraglutide and metformin treatment as a randomised control group (figure below). The randomisation of subjects to treatment groups was stratified by previous treatment with metformin or a combination of metformin and a sulphonylurea.

Subjects not fulfilling the randomisation criterion at the end of the run-in period continued treatment with liraglutide 1.8 mg + metformin in a non-randomised treatment arm.
**Trial Design (Trial 1842)**

The treatment groups were as follows:

Randomised treatments
- Insulin detemir+liraglutide 1.8 mg+metformin ≥1500 mg/day
- Liraglutide 1.8 mg+metformin ≥1500 mg/day

Non-randomised treatment
- Liraglutide 1.8 mg+metformin ≥1500 mg/day

**Liraglutide treatment:**

Liraglutide at a dose of 1.8 mg was chosen for the trial as it is the maximum approved dose. Treatment with liraglutide 1.8 mg also resulted in the highest percentage of subjects reaching the American Diabetes Association target for HbA1c (≤7%) and the greatest weight reduction during the phase 3a program.

**Insulin detemir treatment:**

At randomisation, the start dose of insulin was 10 U. The insulin detemir dose could be adjusted by the investigator at site visits and telephone contacts, based upon the subject’s self-measured fasting plasma glucose measurements (SMPG fasting measurements on three days in the week prior to dose adjustment) according to table below.

**Algorithm for Titration of Insulin Detemir Dose**

<table>
<thead>
<tr>
<th>Average PG in a fasting state used for titration</th>
<th>Increase in insulin dose (Units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 – 6.0 mmol/L (73 – 108 mg/dL) Target</td>
<td>No adjustment</td>
</tr>
<tr>
<td>6.1 – 8.0 mmol/L (109 – 144 mg/dL)</td>
<td>+2</td>
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<tr>
<td>8.1 – 9.0 mmol/L (145 – 162 mg/dL)</td>
<td>+4</td>
</tr>
<tr>
<td>9.1 – 10 mmol/L (163 – 180 mg/dL)</td>
<td>+6</td>
</tr>
<tr>
<td>&gt; 10.0 mmol/L (&gt; 180 mg/dL)</td>
<td>+8</td>
</tr>
</tbody>
</table>

**Metformin treatment:**

Subjects were to continue their current treatment with metformin at a stable, pre-trial dose level and dosing frequency.

The trial design is considered appropriate. The open labelled design is acknowledged as insulin therapy can not be blinded due to titration of therapy guided by plasma glucose levels.

Randomisation to +/- insulin therapy was preceded by a 12 weeks run-in period in which, patients were forced up-titrated to liraglutide 1.8mg during the first 2 weeks. The length of the run-in period is considered sufficient. Randomisation was based on HbA1C ≥ 7.0%. This approach is considered acceptable. The up-titration algorithm for insulin detemir used in the study is considered appropriate and in line with clinical practice.

No rescue therapy was allowed until week 26 for the randomised liraglutide + metformin group. However, appropriate withdrawal criteria based on fasting plasma glucose were pre-specified for the run-in- as well as for the main treatment period.

- **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.
1.1.4.3. Results

2. Participant flow

A total of 988 subjects entered the run-in phase of the trial and all but one of these subjects (withdrew on own initiative and based on high blood glucose), were exposed to liraglutide 1.8 mg + metformin. About 17% (167 of 988) of subjects withdrew early (‘early withdrawals’), i.e. during the run-in period and before randomisation mostly due to adverse events (mainly gastrointestinal adverse events).

498 (60.7%) subjects 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 with an HbA1c ≥ 7% after completing the run-in phase were randomised to receive study treatment. The highest withdrawal rate was observed in the randomised liraglutide 1.8 mg + metformin group, with decreasing rates observed for insulin detemir + liraglutide 1.8 mg + metformin and non-randomised liraglutide 1.8 mg + metformin (21.1%, 11.1% and 5.6%, respectively).

Subject Disposition

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<tr>
<td>Run-in</td>
<td>161</td>
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<tr>
<td>Exposed to Liraglutide</td>
<td>161 (100)</td>
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<tr>
<td>Randomised</td>
<td>161 (100)</td>
</tr>
<tr>
<td>Main</td>
<td>161 (100)</td>
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<tr>
<td>Exposed to Detemir</td>
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<tr>
<td>Withdrawals</td>
<td>34 (21.1)</td>
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<td>Adverse Events</td>
<td>6 (3.7)</td>
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<td>Non-compliance with protocol</td>
<td>3 (1.9)</td>
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<tr>
<td>Withdrawal criteria</td>
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<tr>
<td>Protocol deviations</td>
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<tr>
<td>Loss to follow up</td>
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<tr>
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<td>157 (97.5)</td>
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<tr>
<td>Safety analysis set</td>
<td>159 (98.8)</td>
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</table>

The withdrawal-rate during the run-in period was 17%, thus being close to the expected 20%. The main reason was gastrointestinal AEs (45.8%; mainly nausea and vomiting (29.8% and 16.9%, respectively). It is well known that liraglutide treatment is associated with a high frequency of GI AEs upon initiation of therapy.

The withdrawal rate during the main treatment period was not much higher than expected (25.0%). However, it is noted that almost twice as many in the liraglutide + metformin arm withdrew vs. the liraglutide + metformin + insulin detemir arm. The rate in the latter was twice as high as in the non-randomised liraglutide + metformin group (21.1% vs. 11.1% vs. 5.6%, respectively).

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 (applicable for Spain only: HBA1c ≥ 9% 12 weeks after
randomisation). A higher number of withdrawals in the randomised liraglutide + metformin arm based on poor glycaemic control could be expected. The review of the distribution of the withdrawal criteria by reason and by week since randomisation did not signal a specific pattern in between the three treatment groups.

**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**

Baseline characteristics and demographics were similarly distributed among the liraglutide + metformin group and the liraglutide + metformin + insulin detemir group. BMI was 33.9-34.9kg/m2 reflecting an obese diabetic population with vast the majority of white race (87.6-88.9%).

Diabetes duration was shorter and the proportion of patients on previous metformin monotherapy higher in the non-randomised liraglutide + metformin group vs. the two randomised groups (6.6Y vs. 8.5-8.6Y and 74.5% vs. 50.0-50.3%, respectively). These differences were also reflected by lower baseline HbA1c and FPG in the non-randomised group (7.7% vs. 8.2-8.3% and 9.2mmol/L vs. 10.2-10.3mmol/L, respectively)

**Outcomes and estimation**

**Primary endpoint**

Change in HbA1c:

The primary endpoint was change in HbA1c after 26 weeks of randomised treatment. The primary efficacy analysis was based on the Full Analysis Set.

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 insulin detemir treatment group, after which HbA1c appeared to remain relatively stable.
Mean Change in HbA1c (%) from Run-in to Week 26 - No Imputation – FAS and Non-randomised Treatment Group

In the Full Analysis Set, using LOCF, the estimated mean changes in HbA1c from baseline to Week 26 were -0.51% and +0.02% in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin treatment groups, respectively. The estimated mean changes in HbA1c with no data imputation were comparable to those presented for LOCF.

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%).

These results were further supported by a repeated measurements analysis (RMA) of HbA1c levels after 12 and 26 weeks of randomised treatment (LS mean difference = -0.49% (95%CI: -0.62; -0.36)).

Prior to database lock the applicant discovered that 78 patients had received less than 80 days of liraglutide treatment during the 12W run-in period why the full effect of liraglutide 1.8mg may not have been obtained in a substantial number of the patients. The distribution of these patients was as follows: 11 and 14 patients in the randomised liraglutide + metformin group and liraglutide + metformin + insulin detemir group, respectively and 53 patients in the non-randomised liraglutide + metformin group. To evaluate if this "under-treatment" may have had impact on the efficacy result, further analyses were provided (ANCOVA using LOCF and ANCOVA with no imputation) including only patients with at least 80 days of liraglutide exposure before randomisation. These analyses supported the statistically significant and clinically relevant effect of adding insulin detemir to liraglutide + metformin in insufficiently controlled type 2 diabetic patients..

Secondary endpoints

Proportions of Subjects reaching HbA1c targets

The proportion of subjects achieving pre-defined HbA1c targets (<7% ADA target and ≤6.5% AACE target) at Week 26 is summarised in table below.
Proportion of Subjects with HbA1c <7% and ≤6.5% at Week 26 (LOCF) – Full Analysis Set

<table>
<thead>
<tr>
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<th>Lira 1.8</th>
<th>Detemir + Lira 1.8</th>
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</thead>
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<td></td>
<td>N</td>
<td>n (%)</td>
</tr>
<tr>
<td>Full Analysis Set</td>
<td>157</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Baseline HbA1c ≤ 7.0 %</td>
<td>157</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Week 26 HbA1c ≤ 7.0 %</td>
<td>157</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Week 26 HbA1c ≤ 7.0 % (LOCF)</td>
<td>149</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Baseline HbA1c ≤ 6.5 %</td>
<td>157</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Week 26 HbA1c ≤ 6.5 %</td>
<td>125</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Week 26 HbA1c ≤ 6.5 % (LOCF)</td>
<td>149</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

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

Fasting plasma glucose:

Mean Change in FPG (mmol/L) from Run-in to Week 26 - No Imputation – FAS and Non-randomised Treatment Group

In the Full Analysis Set, using LOCF, the estimated mean reductions in FPG from baseline to Week 26 were 2.12 mmol/L and 0.39 mmol/L in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin treatment groups, respectively. This difference in FPG reduction was statistically significant (estimated treatment difference of -1.73 mmol/L (95%CI: -2.16;-1.30); p<0.0001).

7-point plasma glucose profiles
In both randomised treatment groups estimated mean decreases in post-prandial glucose at all meal times were observed, with the greatest decrease consistently observed with insulin detemir + liraglutide 1.8 mg + metformin (ranging from -1.18 mmol/L to -2.09 mmol/L) vs. liraglutide 1.8mg + metformin (-0.48 mmol/L to -0.97 mmol/L). The estimated mean decrease in post-prandial glucose was statistically significantly greater with insulin detemir + liraglutide 1.8 mg + metformin treatment compared to liraglutide 1.8 mg + metformin treatment alone for all meal times (estimated treatment differences and 95%CIs of -1.12 mmol/L (-1.72;-0.51), -0.60 mmol/L (-1.12;-0.08) and -0.70 mmol/L (-1.25;-0.14) for breakfast, lunch and dinner, respectively).

Statistically significant more subjects in the insulin detemir + liraglutide 1.8mg + metformin group vs. liraglutide 1.8mg + metformin group (approximately 10% difference) had post prandial PG < 10 mmol/L. No statistically significant treatment difference was observed for change in prandial increments at either breakfast, lunch or dinner.

**Bodyweight:**

The greatest reduction in body weight in all treatment groups was observed during the 12-week run-in period (3.5 to 4.3 kg). In the Full Analysis Set, using LOCF, the estimated mean reductions in body weight from baseline to Week 26 were 0.16 kg and 0.95 kg in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin treatment groups, respectively. This difference was statistically significant (estimated treatment difference of 0.79 kg (95%CI: 0.08;1.49); p=0.0283) in favour of the liraglutide 1.8 mg + metformin group. The estimated mean changes in body weight based on completers were comparable to those presented for LOCF (estimated treatment difference of 0.80 kg (95%CI: 0.01;1.59); p=0.0471)
Mean Change in Body Weight (kg) from Run-in to Week 26 - No Imputation - FAS and Non-randomised Treatment Group

![Graph showing body weight change over time]

**Waist and Hip circumference:**

The mean change in waist circumference from baseline to Week 26 was analysed using an ANCOVA model. In the Full Analysis Set, using LOCF, the estimated mean changes in waist circumference from baseline to Week 26 were -0.78 cm and -0.66 cm in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin treatment groups respectively. There was no statistically significant difference in change in waist circumference for the two groups (estimated treatment difference of -0.12 cm (95% CI: -1.17; 0.93); p=0.8229).

In the Full Analysis Set, using LOCF, the estimated mean changes in hip circumference from baseline to Week 26 were -0.38 cm and -0.36 cm in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin treatment groups, respectively. There was no statistically significant difference in change in hip circumference for the two groups (estimated treatment difference of 0.02 cm).

**Beta cell function:**

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 insulin detemir + liraglutide 1.8 mg + metformin group compared to subjects in the liraglutide 1.8 mg + metformin group (P=0.0230 and p<0.0001, respectively). No treatment difference was observed for pro-insulin to C-peptide ratio.

**Fasting lipid profile:**

From baseline to Week 26, there was a statistically significant treatment difference for change in free fatty acids, with estimated decreases of 0.11 mmol/L and 0.03 mmol/L in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin treatment groups, respectively (estimated treatment difference of -0.08 mmol/L). Other statistically significant treatment differences from baseline to Week 26, with respect to fasting lipid profile, were not observed.
Systolic and diastolic blood pressure:

For systolic blood pressure, there was an initial net mean reduction in both treatment groups, however, at Week 26, there appeared to be no change from baseline in subjects treated with insulin detemir + liraglutide 1.8 mg + metformin (LSmean change from baseline using an ANCOVA model and LOCF was +0.41), whereas there was an increase in subjects treated with liraglutide 1.8 mg + metformin (LSmean change from baseline using an ANCOVA model and LOCF was +1.11). The difference between treatment the treatment arms was not statistically significant (estimated treatment difference -0.70 (95% CI: -3.48;2.07); p=0.6192)

The mean change in diastolic blood pressure from baseline to Week 26 was analysed using an ANCOVA model. In the Full Analysis Set, using LOCF, the estimated mean changes in diastolic blood pressure from baseline to Week 26 were -0.40 mmHg and -1.10 mmHg in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin treatment groups, respectively. There was no statistically significant difference in change in diastolic blood pressure between the two groups (estimated treatment difference 0.70 mmHg (95%CI: -1.06; 2.46); p=0.4325)

Additional secondary endpoints

The proportion of subjects reaching target Hb A1c <7%, SBP<130 mmHg and change in body Weight ≤0 kg at Week 26:

A logistic regression was performed for this composite endpoint for randomised subjects. A greater proportion of subjects treated with insulin detemir + liraglutide 1.8 mg + metformin met the specified target versus subjects treated with liraglutide 1.8 mg + metformin alone (10.5% versus 4.1%) and this difference was statistically significant. The corresponding odds ratio was 2.74 (95%CI: 1.24; 6.05); p= 0.0126)

The proportion of patients reaching target Hb A1c <7%, change in body weight ≤0 kg at Week 26 and no major or minor hypoglycaemia during the main period:

A logistic regression was performed for this composite endpoint for randomised subjects. A greater proportion of subjects treated with insulin detemir + liraglutide 1.8 mg + metformin met the specified target versus subjects treated with liraglutide 1.8 mg + metformin alone (21.7% versus 8.9%) and this difference was statistically significant. The corresponding odds ratio 2.82 (95% CI: 1.51; 5.28); p=0.0012)

The secondary endpoints were all of only supportive evidence to the primary endpoint. No adjustment for multiplicity was applied in the analyses of the secondary endpoints.

Proportion of subjects reaching HbA1c targets: It was noticed that one patient was wrongly randomised to treatment (i.e. baseline HbA1c below 7.0%). This patient was randomised to liraglutide + metformin treatment. However it was not believed to have had overall impact on the efficacy results. The data from this analysis seem to support the superior efficacy of liraglutide + metformin + insulin detemir; based on a logistic regression model with treatment as fixed effect and baseline HbA1c as a covariate. The liraglutide + metformin + insulin detemir arm was statistically significantly superior to liraglutide + metformin on reaching the target HbA1c < 7.0% (20.1% vs. 44.4%; OR=3.75 (95%CI: 2.19;6.45); p<0.0001) and HbA1c<6.5% (19.4% vs. 7.4%; OR=3.32 (95%CI: 1.59;7.00); p=0.0016). This effect seemed independent of baseline HbA1c (<7.5%, ≥ 7.5% to < 8.0%; ≥8.0%) though the percentage of patients reaching the targets in both treatment groups was lower when baseline HbA1c increased.

Fasting plasma glucose: The effect on fasting plasma glucose was largest for all 3 treatment groups (the two randomised groups and the non-randomised liraglutide + metformin group) during the run-in
period in which liraglutide 1.8mg treatment was initiated. Based on the analysis performed liraglutide + metformin + insulin detemir was statistically significantly superior to liraglutide + metformin for change in FPG from randomisation to week 26 (treatment difference of -1.73 mmol/L (95%CI: -2.16; -1.30); p<0.0001).

7-point self measured plasma glucose profile: At week 26 both randomised treatment groups had reductions in the 7-point self measured plasma glucose profile when compared to randomisation (week 0). The post-prandial PG reductions at week 26 were statistically significantly greater for liraglutide +metformin +insulin detemir vs. liraglutide + metformin alone (estimated treatment differences and 95% CIs of -1.12 mmol/L (-1.72;-0.51), -0.60 mmol/L (-1.12;-0.08) and -0.70 mmol/L (-1.25;-0.14) for breakfast, lunch and dinner, respectively).

Bodyweight: Although statistically significant, body weight reductions from randomisation to week 26 were small and hardly of large clinical impact the estimated mean reductions in body weight were 0.16 kg and 0.95 kg in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin treatment groups, respectively. Still, the data on bodyweight indicate that the decrease in bodyweight observed during the run-in period was sustained throughout the 26 weeks maintenance period.

Waist and Hip circumference: There was no statistically significant difference in change in waist or hip circumference for the two groups (estimated treatment differences were -0.12 cm (95% CI: -1.17; 0.93); p=0.8229) and 0.02 cm for waist and hip circumference, respectively.

Beta cell function: The effects of treatments on HOMA index of β-cell function, and HOMA index of insulin resistance were not established in this study due to cross-reactivity between insulin detemir and the insulin assay. However, these measures are considered inadequate measures of beta-cell function as they are based on fasting values of plasma insulin and glucose why interpretation of such results should be made with caution (in fact the HOMA-IR is a measure of insulin resistance and not insulin secretion). For a more precise evaluation of the impact on the pancreatic beta-cell function dynamic estimates from IVGTT, clamps or standardised mixed meal test would be necessary.

Fasting lipid profile: No clinically relevant differences were observed between the randomised treatment groups in fasting lipid profile (total cholesterol, LDL, VLDL, HDL, triglycerides or free fatty acids

Systolic and diastolic blood pressure: There were no statistically significant differences in systolic or diastolic blood pressure between the two randomised treatment arms.

2.1.1.1. Clinical studies in special populations

N/A

2.1.1.2. Supportive studies

See clinical pharmacology section

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

N/A
2.2. CHMP overall conclusions on clinical efficacy

The efficacy of insulin detemir (levemir) as add-on to liraglutide 1.8mg and metformin was evaluated in a 26 weeks randomised, open-label, two-armed, parallel-group, multicentre, multinational trial (proceed by a 12 weeks run-in) with a 26-week extension.

Type 2 diabetic patients insufficiently controlled on metformin- (≥ 1500mg/day) or metformin + SU (½ maximum dose) were included in the 12 weeks run-in period during which, liraglutide was forced titrated to 1.8mg/day. The first group reflects a typical add-on design and is according to daily clinical practice. The latter group (metformin + SU) represents however 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 was considered acceptable.

The criterion for randomisation to the main 26 weeks treatment period (+/- insulin therapy) was an HbA1C ≥ 7.0%. Patients who did not fulfil the randomisation criterion at the end of the run-in period (i.e. HbA1c < 7.0%), continued treatment with liraglutide 1.8 mg + metformin in a non-randomised treatment arm. This treatment arm was included to evaluate the long-term sustainability of glycaemic control and safety data.

The non-randomised arm comprised 499 patients, the randomised liraglutide + metformin arm comprised 161 patients and the randomised insulin detemir + liraglutide + metformin arm comprised 162 patients.

The up-titration algorithm for insulin detemir used in the study is considered appropriate. In the response to the RSI it was confirmed that appropriate actions were taken during the study to ensure compliance to metformin treatment. No rescue therapy was allowed until week 26 for the randomised liraglutide + metformin group. However, appropriate withdrawal criteria based on fasting plasma glucose were pre-specified for the run-in- as well as for the main treatment period.

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 primary endpoint was analysed using the full analysis set and an analysis of covariance (ANCOVA) of change in HbA1c from randomisation to Week 26 for the randomised treatment groups. Treatment, previous OAD and country were explanatory variables and randomisation HbA1c values were included as covariates. The statistical approach was considered acceptable.

Missing observations were considered missing at random in all analyses and missing values at post baseline visits were replaced using LOCF. Expecting that the largest effect of liraglutide 1.8mg is obtained during the 12 weeks run-un period, CHMP agree that LOCF seem to be the most conservative way to address drop-outs in this study.

The withdrawal rate during the main treatment period was not much higher than expected (25.0%) however; almost twice as many in the liraglutide + metformin arm withdrew vs. the liraglutide + metformin + insulin detemir arm. In the response to the RSI further clarification was provided. The number of withdrawals by reason and by week after randomisation did not signal a specific pattern between the three treatment groups. Neither did the graphical presentations by withdrawal reason and by week since randomisation cause any concerns.

Baseline characteristics and demographics were similarly distributed among the liraglutide + metformin group and the liraglutide + metformin + insulin detemir group. BMI was 33.9-34.9kg/m² thus, reflecting an obese diabetic population with vast the majority of white race (87.6-88.9%).
Not surprisingly, diabetes duration was shorter and the proportion of patients on previous metformin monotherapy higher in the non-randomised liraglutide + metformin group vs. the two randomised groups (6.6Y vs. 8.5-8.6Y and 74.5% vs. 50.0-50.3%, respectively). These differences were also reflected by lower baseline HbA1c and FPG in the non-randomised group (7.7% vs. 8.2-8.3% and 9.2mmol/L vs. 10.2-10.3mmol/L, respectively).

Treatment with liraglutide + metformin +insulin detemir resulted in a statistically significant and clinically relevant decrease in HbA1c after 26 weeks treatment (primary endpoint) when compared to liraglutide + metformin (LSMean difference = -0.52% (95% CI: -0.68;-0.36), P<0.0001).

11 and 14 patients in the liraglutide + metformin and liraglutide + metformin + insulin detemir, respectively had received less than 80 days of liraglutide treatment during the 12W run-in period. Additional confirmation of efficacy was provided in the answer to the RSI. The results of the supportive analyses of the full analysis set comprising only patients with at least 80 days of exposure before randomisation (ANCOVA of Change in HbA1c (%) – LOCF and ANCOVA of Change in HbA1c (%) - No Imputation) were similar to the results of the primary analysis of the primary endpoint (analysis of covariance (ANCOVA) of change in HbA1c from randomisation to Week 26 using LOCF for missing data).

The secondary endpoints were all of only supportive evidence to the primary endpoint. No adjustment for multiplicity was applied in the analyses of the secondary endpoints.

The superior efficacy of liraglutide + metformin + insulin detemir vs. liraglutide + metformin on primary endpoint was further supported by other endpoints reflecting glycaemic control. Liraglutide + metformin + insulin detemir was statistically significantly superior to liraglutide + metformin on reaching the target \( \text{HbA1c} < 7.0\% \) (20.1% vs. 44.4%; OR=3.75 (95%CI: 2.19;6.45); p<0.0001) and \( \text{HbA1c}<6.5\% \) (19.4% vs. 7.4%; OR=3.32 (95%CI: 1.59;7.00); p=0.0016). In addition, liraglutide + metformin + insulin detemir was statistically significantly superior to liraglutide + metformin for change in FPG (treatment difference of -1.73 mmol/L (95%CI: -2.16;-1.30); p<0.0001) and in post-prandial PG reductions from randomisation to week 26 (estimated treatment differences and 95%CIs of -1.12 mmol/L (-1.72;-0.51), -0.60 mmol/L (-1.12;-0.08) and -0.70 mmol/L (-1.25;-0.14) for breakfast, lunch and dinner, respectively).

The estimated mean reductions in body weight from randomisation to Week 26 were 0.16 kg and 0.95 kg in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin treatment groups, respectively. The difference in body weight reduction was statistically significant (estimated treatment difference of 0.79 kg) in favour of the liraglutide 1.8 mg + metformin group but the observed very small reduction in body weight is hardly of clinical relevance. Still, the data on bodyweight indicate that the decrease in bodyweight observed during the run-in period was sustained throughout the 26 weeks maintenance period. There was no statistically significant difference in change in waist or hip circumference for the two groups after randomisation.

Potential differences in treatment effect on beta cell function could not be assessed in this study (HOMA-B and HOMA-IR) due to cross-reactivity between insulin detemir and the insulin assay. No clinically relevant differences were observed between the randomised treatment groups in fasting lipid profile (total cholesterol, LDL, VLDL, HDL, triglycerides or free fatty acids) after randomisation.

There were no statistically significant differences in systolic or diastolic blood pressure between the two randomised treatment arms.
Conclusions on clinical efficacy

The triple therapy regimen (insulin detemir + liraglutide + metformin) had a statistically significant superior effect on decrease in 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. From an efficacy point of view, the benefit of insulin detemir when added to treatment with liraglutide 1.8mg + metformin (≥ 1500mg/day) in type 2 diabetic patients insufficiently controlled on this dual therapy is considered of clinical relevance.

2.2.1. Clinical safety

2.2.1.1. Patient exposure

In trial 1843 987 subjects were exposed to trial products.

Mean duration of insulin detemir treatment was 173.2 days and with a total subject exposure time of 76.8 years.

The greatest liraglutide exposure was in the nonrandomised liraglutide 1.8 mg + metformin group (mean duration of 263.2 days). For the randomised treatment groups, mean duration of liraglutide treatment was slightly higher in subjects treated with the insulin detemir + liraglutide 1.8 mg + metformin vs. that for subjects treated with liraglutide 1.8 mg + metformin (mean 259.7 days vs. 247.7 days). These exposure differences are also reflected in “total liraglutide exposure in subject years” (nonrandomised liraglutide + metformin: 359.6; detemir + liraglutide + metformin: 115.9; liraglutide + metformin: 107.8).

In trial 3673, Thirty-three (33) subjects (100%) were exposed to at least one dose of trial drug. Of these, 32 subjects received both insulin detemir (single dose of 0.5 units [U]/kg on Day 1 and Day 36) and liraglutide 0.6, 1.2, and 1.8 mg doses (1.8 mg dose over liraglutide maintenance period) during the trial.

2.2.1.2. Adverse events

The safety profile of insulin detemir (Trial 1842) in the treatment arm where insulin detemir was used in combination with liraglutide and metformin was in line with the overall safety profile previously reported for insulin detemir OAD combinations (EMEA/HC/528/II/0016)

In Trial 1842, the most commonly reported adverse events in all treatment groups and for the entire trial period were nausea and diarrhoea within the system organ class gastrointestinal disorders (17.2%, 23.3%, 25.5% and 16.6%, 15.1%, 12.0% in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin and the nonrandomised treatment groups, respectively). Nasopharyngitis, within the system organ class infections and infestations, was also common in all treatment groups, and affecting a slightly higher proportion of subjects in the randomised liraglutide 1.8 mg + metformin group versus the insulin detemir + liraglutide 1.8 mg + metformin and the nonrandomised liraglutide 1.8 mg + metformin treatment group (20.8% versus 14.7% and 11.0%). Tables below summarises the AEs during the the main period respectively.

The proportion of early withdrawal subjects reporting gastrointestinal disorders, specifically nausea, diarrhoea and vomiting, was consistently higher compared with subjects continuing into the main period of the trial.
Trial 1842 – Treatment-emergent Adverse Events with an Incidence >5% of Subjects in Any Treatment during Main Period by System Organ Class and Preferred Term – Safety Analysis Set

| Abbreviations: % = proportion of subjects in analysis set having adverse event; Detemir = insulin detemir; E = number of adverse events; Early WD = withdrawals before randomisation visit (Visit 4b); Lira = liraglutide; N = number of subjects with adverse event. |

Disregarding the early withdrawal group, the majority of adverse events in all treatment groups were mild (67.9% or more of all adverse events reported in each treatment group) or moderate (33% or more of all adverse events reported in each treatment group). The incidence of severe adverse events was also comparable between all three treatment groups and ranged from 6.3% to 8.0%.

The majority of adverse events were unlikely related to trial products, as assessed by the investigator (67% or more of all adverse events reported in each treatment group).

Adverse events by SOC or syndrome:

In trial 1842 the following adverse events were pre-specified as adverse events of special interest: Medication errors, suspected transmission of an infectious agent, pancreatitis and related events, thyroid gland disorders, injection site reactions, neoplasm and major hypoglycaemic events. No events of suspected transmission of an infectious agent via a trial product were reported.

A total of 34 events classified as medication errors were reported including incorrect dose administered, accidental overdose, inappropriate schedule of drug administration, overdose, wrong drug administered, underdose, wrong technique in drug usage process, adverse drug reaction and device misuse. Most events were reported by single subjects, and no major treatment group difference was apparent. More subjects in the insulin detemir + liraglutide 1.8mg + metformin group reported “incorrect dose” administered compared to the other groups in which liraglutide was administered alone (2.5% vs. 0%-1.8%)

The overall proportion of subjects reporting pancreas-related adverse events was slightly higher in the insulin detemir + liraglutide 1.8 mg + metformin group vs. the liraglutide 1.8 mg + metformin group (11.0% vs. 7.5%, respectively).

The most commonly reported pancreas related adverse event was increased lipase, reported by similar proportions of subjects within the treatment groups.
Trial 1842 – Pancreas-related Treatment-emergent Adverse Event by System Organ Class and Preferred Term – Safety Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>Lira 1.8 (%)</th>
<th>Detemir + Lira 1.8 (%)</th>
<th>Nonrandomised (%)</th>
<th>Early WD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Analysis Set</td>
<td>159 (33.6)</td>
<td>163 (33.3)</td>
<td>499 (33.0)</td>
<td>166 (33.0)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>12 (7.5)</td>
<td>13 (8.9)</td>
<td>27 (5.4)</td>
<td>20 (6.6)</td>
</tr>
<tr>
<td>Investigations</td>
<td>11 (6.9)</td>
<td>12 (8.8)</td>
<td>27 (5.4)</td>
<td>20 (6.6)</td>
</tr>
<tr>
<td>Lipase Increased</td>
<td>11 (6.9)</td>
<td>12 (8.8)</td>
<td>26 (5.2)</td>
<td>10 (6.0)</td>
</tr>
<tr>
<td>Blood Amylase Increased</td>
<td>2 (0.4)</td>
<td>2 (0.4)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Pancreatic Disorder</td>
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<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Pancreatitis Chronic</td>
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<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Thyroid Neoplasm</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

Note: All subjects also received metformin.

Two cases of pancreatitis were reported by 2 subjects during the trial period, in the liraglutide + metformin group, and early withdrawal group, respectively. Both events were judged possibly drug related.

The overall proportion of subjects reporting thyroid-related adverse events was low and comparable across treatment groups: 1.2% (insulin detemir + liraglutide 1.8 mg + metformin), 1.9% (liraglutide 1.8 mg + metformin) and 2.4% (non-randomised liraglutide 1.8 mg + metformin), respectively. The most frequently reported thyroid-related adverse event in all treatment groups was increased calcitonin. No treatment difference in the reporting of this event was observed.

One case of thyroid cancer was reported during the run-in period. A second case was initially reported during the run-in period as well, however this event was re-coded on the basis of up-dated information from the investigator. No events of medullary thyroid cancer were observed in any of the treatments.

Trial 1842 – Thyroid-related Treatment-emergent Adverse Event by System

Organ Class and Preferred Term – Safety Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>Lira 1.8 (%)</th>
<th>Detemir + Lira 1.8 (%)</th>
<th>Nonrandomised (%)</th>
<th>Early WD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Analysis Set</td>
<td>159 (33.6)</td>
<td>163 (33.3)</td>
<td>499 (33.0)</td>
<td>166 (33.0)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>3 (1.5)</td>
<td>2 (1.2)</td>
<td>12 (2.4)</td>
<td>2 (1.2)</td>
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<tr>
<td>Endocrine disorders</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>5 (1.0)</td>
<td>3 (0.4)</td>
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<tr>
<td>Tumors</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>2 (0.4)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Blood Calcitonin Increased</td>
<td>3 (1.9)</td>
<td>1 (0.6)</td>
<td>7 (1.4)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Thyroid Neoplasm</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

Note: All subjects also received metformin.

Abbreviations: % = proportion of subjects in analysis set having adverse event; E = number of adverse events; Detemir = insulin detemir; Early WD = withdrawals before randomisation visit (Visit 4b); Lira = liraglutide; N = number of subjects with adverse event.
**Injection site reactions** can occur with any insulin injection (frequency 1-10%) however, the event is more frequently related to insulin detemir than human insulin. If a subject experienced an injection site reaction, an adverse event form was to be filled in. A list of further clarifications in addition to the date and timing of insulin detemir doses in the preceding 24 hours were to be included in the eCRF. The reported events were all nonserious injection site reactions (5 of 8) and injection site haematomas (3 of 8). All but 1 event was mild (1 event was moderate), and none of the events led to either insulin detemir or liraglutide dose changes. All but 1 subject recovered.

Thirteen **neoplasm adverse events** were reported by 12 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. There were 4 subjects reporting cancer, one of which was thyroid cancer (discussed above).

**Trial 1842 – Neoplasm-related Treatment-emergent Adverse Event by System Organ Class and Preferred Term – Safety Analysis Set**

<table>
<thead>
<tr>
<th>Safety Analysis Set</th>
<th>Lira 1.8 (%)</th>
<th>Detemir + Lira 1.8 (%)</th>
<th>Nonrandomised (%)</th>
<th>Early WD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>E</td>
<td>E</td>
<td>N</td>
<td>E</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>145 (0.6)</td>
<td>11 (0.0)</td>
<td>11 (0.6)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>10 (0.6)</td>
<td>10 (0.6)</td>
<td>10 (0.6)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>1 (0.2)</td>
<td>1 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Breast Neoplasm</td>
<td>1 (0.2)</td>
<td>1 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Fibroma</td>
<td>2 (0.4)</td>
<td>2 (0.2)</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Lipoma</td>
<td>1 (0.2)</td>
<td>1 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Melanocytic Nevus</td>
<td>1 (0.2)</td>
<td>1 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Metastases to Central Nervous System</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Renal Cancer</td>
<td>1 (0.2)</td>
<td>1 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Skin Papilloma</td>
<td>1 (0.2)</td>
<td>1 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>1 (0.2)</td>
<td>1 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Uterine Leiomyoma</td>
<td>2 (0.4)</td>
<td>2 (0.2)</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
</tr>
</tbody>
</table>

Note: All subjects also received metformin.

Abbreviations: % = proportion of subjects in analysis set having adverse event; E = number of adverse events; Detemir = insulin detemir; Early WD = withdrawals before randomisation visit (Visit 4b); Lira = liraglutide; N = number of subjects with adverse event.

No major hypoglycaemic episodes or withdrawals due to hypoglycaemic episodes were reported in the insulin detemir + liraglutide 1.8 mg + metformin treatment group. The analysis of hypoglycaemic episodes during the main period (excluding an outlier with 24 minor and symptoms only hypoglycaemic episodes, liraglutide + metformin group) confirmed a low incidence in all treatment groups (0.224 and 0.019 events per subject year for insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin control group, respectively). The rate of minor hypoglycaemic episodes reported during the main period, excluding the outlier, was compared for the two randomised treatment groups in Table 2–14. The rate of both all episodes and minor hypoglycaemic episodes was statistically significantly higher in the insulin detemir + liraglutide 1.8 mg + metformin treated subjects compared to the liraglutide 1.8 mg + metformin treated subjects (p = 0.0108 and p = 0.0075, respectively). When including the outlier, no statistically significant treatment differences were observed.
Trial 1842 – Summary of Treatment-emergent Hypoglycaemic Episodes during Main Period Excluding Outlier – Safety Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide 1.8</th>
<th>Insulin Detemir + Liraglutide 1.8</th>
<th>Nonrandomised group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N   (%)</td>
<td>E   R</td>
<td>N   (%)</td>
</tr>
<tr>
<td>Safety analysis set</td>
<td>159</td>
<td>163</td>
<td>499</td>
</tr>
<tr>
<td>Exposure liraglutide (subject years)</td>
<td>69</td>
<td>77</td>
<td>.</td>
</tr>
<tr>
<td>Exposure detemir (subject years)</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Major</td>
<td>0 ( 0.0)</td>
<td>0 0.000</td>
<td>0 ( 0.0)</td>
</tr>
<tr>
<td>Minor</td>
<td>2 ( 1.3)</td>
<td>2 0.029</td>
<td>13 ( 8.0)</td>
</tr>
</tbody>
</table>

Note. All arms also received metformin. Subject 916005 is an outlier and excluded due to extreme number of hypoglycaemic episodes.

Abbreviations: % = proportion of subjects in analysis set having adverse events; E = number of adverse events; N = number of subjects with adverse events; R = episodes per subject year (liraglutide).

Trial 1842 – Analysis of Hypoglycaemic Episodes during Main Period Excluding Outlier – Safety Analysis Set

<table>
<thead>
<tr>
<th>Treatment / Comparison</th>
<th>Rate Ratio (Insulin Detemir + Liraglutide 1.8 / Liraglutide 1.8)</th>
<th>Estimates</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin detemir + liraglutide 1.8 - liraglutide 1.8</td>
<td>3.13</td>
<td>[ 1.30 ;  7.54]</td>
<td>0.0108</td>
<td></td>
</tr>
<tr>
<td>Minor episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin detemir + liraglutide 1.8 - liraglutide 1.8</td>
<td>8.57</td>
<td>[ 1.78 ; 41.37]</td>
<td>0.0075</td>
<td></td>
</tr>
</tbody>
</table>

Note: All subjects also received metformin. The estimated rate of episodes is from a negative binomial model with treatment as fixed effect. The model is not estimable for symptomatic, major and unknown episodes. Subject 916005 is an outlier and excluded due to extreme number of hypoglycaemic episodes.

Abbreviation: CI = confidence interval.

The overall pattern and frequencies of the most common adverse events when insulin detemir was added to the combination of liraglutide 1.8mg + metformin was similar to the overall safety profile observed for insulin detemir in combination with other OAD.

During the run-in period the most common AEs were GI events, nausea, vomiting, diarrhoea, dyspepsia, and upper abdominal pain. These were markedly highest in those subjects withdrawing early (i.e. in the run-in period) and lowest in the insulin detemir + liraglutide + metformin group. In the main period diarrhoea and nausea were lowest in the non-randomised group. A clear pattern was thus not evident. The data support the notion also reported in the original MAA for liraglutide, that the incidence of liraglutide induced nausea for most subjects is transient, with the highest number of subject reporting nausea during the up-titration phase of liraglutide treatment (data not shown here).

Several adverse events were pre-specified as medical events of special interest (MESIs) most of them originating from the original MAA for liraglutide.
Medication errors: medication errors were relevantly included as MESIs; the more medications taken concomitantly the greater the risk for these events may potentially be. In between treatment groups the only difference observed (though small) was on “incorrect dose administered”, the highest proportion observed in the insulin detemir + liraglutide + metformin group (2.5% vs. 0%, 1.0% and 1.8% in the randomised and non-randomised liraglutide + metformin groups and early withdrawal group). These medication errors were however not associated with major hypoglycaemic events.

Pancreas related events: The overall incidence of pancreas-related TEAEs was higher in the insulin detemir + liraglutide + metformin group (11.0%) when compared the randomised and non-randomised liraglutide + metformin groups and the “early withdrawal” group (7.5%, 5.4% and 6.0%). The increased incidence was mainly related to increases in blood lipase (please refer to further discussion in section on laboratory findings). These parameters were not part of the routine safety laboratory parameters in the original liraglutide MAA why previous experience on this issue does not exist.

Treatment with GLP1 analogues seems rarely associated with pancreatitis. The 2 events reported in this trial is thus, not a new safety signal and do correspond to the frequency observed during the long term trials in the original MAA for liraglutide (0.2%) – notably the events did not occur in the insulin detemir + liraglutide + metformin group.

Thyroid related AEs were comparable across treatment groups and was overall comparable to the frequency observed in the original liraglutide MAA. Notable the events of “increased calcitonin levels” and the single event of thyroid cancer (papillary thyroid cancer) were not observed in the insulin detemir + liraglutide + metformin group. In addition no cases of medullary thyroid cancer were reported. However, the study was of limited duration.

Injection site reactions: Injection site reactions with levemir were in the range of what is known from previous experience.

Hypoglycaemic events: There were no major hypoglycaemic episodes. Minor hypoglycaemic events occurred significantly more frequent in the insulin detemir + liraglutide group (8% of subjects) compared to the other treatment groups (liraglutide + metformin 1.3%, non-randomised liraglutide + metformin 3.8%). The frequency of minor hypoglycaemic events is not higher than that observed for insulin detemir in the original MAA.

Cardiovascular safety: Based on the original dossier cardiac events represents 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.

### 2.2.1.3. Serious adverse events and deaths

No deaths were reported in Trial 1842 (12-week run-in and 26-week main treatment period) or trial 3673.

In trial 3673 no treatment-emergent serious adverse events were reported.

In trial 1842 the overall proportion of subjects reporting serious adverse events was low and comparable across treatment groups (5.5%, 5.0% and 7.8% in the insulin detemir + liraglutide 1.8 mg + metformin- and randomised and nonrandomised liraglutide 1.8 mg + metformin groups, respectively).

The incidence of severe, moderate and mild serious adverse events was also comparable across treatment groups, with the overall proportion of subjects reporting severe adverse events being 3.7%,
3.1% and 4.2% for the insulin detemir + liraglutide 1.8 mg + metformin- and randomised and nonrandomised liraglutide 1.8 mg + metformin groups, respectively.

Overall, most serious adverse events were reported by single subjects only and were spread across several system organ classes, with the majority in the SOC injury, poisoning and procedural complications: for the latter, 12 events in total were reported with equal proportions in the insulin detemir + liraglutide 1.8 mg + metformin- and nonrandomised liraglutide 1.8 mg + metformin groups (1.2% and 1.6%, respectively) and none in the liraglutide 1.8 mg + metformin group.

The serious adverse events thought by the investigators to be possibly or probably related to trial product were few (8 in total for both run-in and main period), and of note, there were no serious adverse events with suspected trial drug causality in the insulin detemir + liraglutide 1.8 mg + metformin group.

There were 11 SAEs reported in 8 patients (5.0%) in the liraglutide + metformin group, 14 SAEs in 9 patients (5.5%) in the insulin detemir + liraglutide + metformin group, 49 AEs in 39 patients (7.8%) in the non-randomised group, and 5 SAEs in 5 patients (3.0%) in the early withdrawal group. No clustering was evident for any of the treatment groups. Notably there was no SAE considered as probably or possibly related to study medication in the insulin detemir + liraglutide + metformin group.

The 2 events of pancreatitis and a single event of suspected c-cell carcinoma – which subsequently could not be confirmed (please refer to discussion of these events above) - do not give rise to new safety concerns.

**Laboratory findings**

Clinical laboratory testing in haematology and biochemistry/clinical chemistry (including calcitonin) and urinanalysis were performed in Trial 1842:

The risk of pancreatitis has been associated with glucagon-like peptide-1 (GLP-1) receptor agonists; therefore regular lipase and amylase measurements were included as part of the laboratory safety assessments in the trial. Values above three times their respective UNRs and/or abdominal pain and/or characteristic findings on CT or magnetic resonance imaging (MRI) were prespecified criteria for pancreatitis (2 out of 3 criteria were to be fulfilled). Patients with symptoms fulfilling the criteria for pancreatitis were withdrawn from the trial.

**Haematology**: No clinically relevant changes or relevant treatment group differences were observed.

**Biochemistry/Clinical Chemistry**:

*Serum lipase*: A small increase in median lipase levels from run-in to Week 26 within normal range was observed in all three treatment groups, with no apparent difference between the groups. The median lipase levels at start of run-in and prior to trial drug administration were 43.0 U/L and 40.5 U/L in the two randomised groups and at Week 26 (after run-in + main = 38 weeks of treatment), these median values were 54.0 U/L and 51.0 U/L, respectively, for subjects in the insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin groups.

The UNL of the assay used for lipase measurements in healthy subjects was 60 U/L. Based on the high values observed for the subjects with type 2 diabetes already before run-in, the UNL for healthy subjects may not be directly transferable.

Significant serum lipase and amylase elevations may be diagnostic of pancreatitis (levels usually above three times the UNL), yet the prevalence in patients with type 2 diabetes mellitus is not well characterised. Upon entering the trial and before trial drug treatment, 21/977 (2.15%) of subjects had a lipase level above three times the upper normal limit, whereas 20/961 (2.08%) and 12/798 (1.50%)
of subjects had lipase above three times the upper normal limit at Weeks 0 and 26 (or at early withdrawal). None of these subjects reported gastrointestinal adverse events at Week 26.

The most common clinical laboratory adverse event in all treatment groups was increased lipase (investigations), reported by 11.0%, 3.8% and 3.4% for subjects treated with insulin detemir + liraglutide 1.8 mg + metformin, liraglutide 1.8 mg + metformin and non-randomised liraglutide 1.8 mg + metformin, respectively (26-week main period).

Fluctuations in lipase values over time were observed in all groups.

More investigators reported increased lipase as an adverse event for subjects in the insulin detemir + liraglutide 1.8 mg + metformin group, however, considering the laboratory values as discussed above, there appeared to be no difference between the treatment groups.

For amylase, a similar, but less pronounced, mean increase was observed for amylase in all three treatment groups.

In Trial 1842, mean calcitonin at Week 26 had increased with 1.15 ng/L and 1.12 ng/L in the liraglutide 1.8 mg + metformin and the insulin detemir + liraglutide 1.8 mg + metformin treatment groups, respectively. No statistically significant treatment difference was observed for the change in calcitonin over time. Furthermore, no treatment difference in calcitonin shifts for subjects with either persistent or incidental calcitonin increases during the 26-week main period was apparent.

### 2.2.1.4. Safety in special populations

No new information is included.

**Immunological events**

Insulin detemir antibody levels were assessed at Week 0 and at Week 26 by a radioimmunoassay. Overall, levels of antibodies specific to insulin detemir remained low during the trial (mean 1.59% B/T at Week 0 and mean 2.20% B/T at Week 26). Small increases were observed from Week 0 (baseline) to Week 26 in antibodies with cross-reacting effect (mean -0.10% B/T at Week 0 and mean 3.89% B/T at Week 26). According to a scatter plot (not shown here) there was no correlation between change in insulin detemir specific antibody titres and change in HbA1c for subjects treated with insulin detemir + liraglutide 1.8 mg metformin. Also, no correlation was observed for antibodies demonstrating cross-reactivity with insulin detemir versus change in HbA1c.

Liraglutide antibody levels were assessed at Week -12, Week 0 and at Week 26 by a radioimmunoassay. At run-in (Week -12), no subjects tested positive for liraglutide antibodies. At Week 0 (baseline), 1 subject in each group was positive for liraglutide antibodies; however, no neutralising effect on liraglutide or cross-reactivity towards native GLP-1 was observed. At Week 26, 2 and 3 subjects, treated with insulin detemir + liraglutide 1.8 mg + metformin and non-randomised liraglutide 1.8 mg + metformin, respectively, were positive for liraglutide antibodies. All but 1 subject in the latter group had antibodies demonstrating cross-reactivity towards native GLP-1. No in vitro neutralising effect was observed. Finally, 2 subjects were positive for liraglutide antibodies (treated with insulin detemir + liraglutide 1.8 mg + metformin and nonrandomised liraglutide 1.8 mg + metformin, respectively); both of whom had antibodies demonstrating cross-reactivity and 1 of whom also demonstrated in vitro neutralising effect. Both subjects withdrew from the trial.

According to a scatter plot (not shown here) there was no correlation between change in liraglutide antibody titres and change in HbA1c for any of the two randomised treatment groups or for the nonrandomised treatment group.
2.2.1.5. Safety related to drug-drug interactions and other interactions

An interaction study with liraglutide and Levemir was conducted, no pharmacokinetic or pharmacodynamic interaction was observed.

2.2.1.6. Discontinuation due to adverse events

In trial 1842, in total, 111 out of 987 subjects (11.2%) exposed to liraglutide withdrew or were withdrawn from the trial period (run-in and main 26-week period) due to adverse events. Except for the early withdrawals, no treatment difference or clustering in type of adverse event withdrawals were observed.

Most withdrawals occurred during the 12-week run-in period of the trial, with about 50% of all withdrawals taking place during this time. Of these early withdrawals, 45.8% of subjects withdrew due to gastrointestinal symptoms, the most common being nausea and vomiting. Furthermore, general disorders and administration site conditions were reported by 10.8% of the early withdrawn subjects, with asthenia being the most common event.

During the main period, the overall proportion of subjects reporting adverse events leading to withdrawal was low and comparable for the two randomised treatment groups, at 2.5% and 3.1% for insulin detemir + liraglutide 1.8 mg + metformin and liraglutide 1.8 mg + metformin, respectively. The withdrawal rate among subjects in the nonrandomised treatment group was somewhat lower compared to the two randomised groups, at 1.0%. Generally, the adverse events leading to withdrawal were reported by single subjects and across system organ classes, with no clustering of events.

No preponderance of discontinuations due to AEs in the insulin detemir + liraglutide + metformin group was seen.

2.2.1.7. Post marketing experience

Post-marketing experience has been provided in terms 64 spontaneous reports arising from off-label use of insulin detemir and liraglutide combination therapy. Of these reports only 21 were medically confirmed. The limited information does not allow any conclusions to be drawn regarding the safety profile when the 2 medicinal products are combined. No new safety signals seem to have emerged based on the data from the off-label use.

2.2.1.8. Incidence of malignant neoplasms in the triple combination arm

It is acknowledged that Levemir (insulin detemir), when used as monotherapy does not seem to have an increased risk of neoplasms. However when 52 weeks safety data were submitted in response to the RSI it became apparent that the percentage patients with malignant events was higher in the triple combination arm (3.1%) compared to the pooled liraglutide + metformin arms (0.76%).

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 (data are only submitted as preliminary data in the response document). 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 glargine, 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 NN sponsored randomised trials in 8693 patients (Dejgaard, Diabetologia 2009) where patients treated 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, final conclusions on a potential risk of insulin detemir and liraglutide cannot be drawn from the current study.

The potential signal of a tumour promoting risk is not as strong as to advice against the use of detemir as add-on to liraglutide + metformin. It is, however, considered 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, the signal of a potential tumour promoting effect seems not as strong as to advice against the use of this combination treatment. In this respect the devastating effects of insufficiently controlled diabetes should be weighed against this potential risk. The PV measures have been implemented in the RMP.

2.2.2. CHMP overall conclusions on clinical safety

In trial 1843, 987 subjects were exposed to trial products.

Mean duration of insulin detemir + liraglutide 1.8mg + metformin treatment was 173.2 days and with a total subject exposure time of 76.8 years. The overall pattern and frequencies of the most common adverse events in trial 1842 when insulin detemir was added to the combination of liraglutide 1.8mg + metformin was similar to the overall safety profile observed for insulin detemir in combination with other OAD. The overall safety profile was further confirmed by week 52 safety data.

During the run-in period the most common AEs were GI events, nausea, vomiting, diarrhoea, dyspepsia, and upper abdominal pain. These were markedly highest in those subjects withdrawing early (i.e. in the run-in period) and lowest in the insulin detemir + liraglutide +metformin group. In the main period diarrhoea and nausea were lowest in the non-randomised group. A clear pattern for GI AEs was thus not evident. The data support the notion also reported in the original MAA for liraglutide, that the incidence of nausea for most subjects is transient, with the highest number of subject reporting nausea during the up-titration phase of liraglutide treatment. The AE-profile has however, only been presented for AEs occurring in >5% of patients. In the response to the RSI, tables presenting TEAES with incidences >1% of subjects were provided. No new safety concerns compared 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: Medication errors, pancreas related events, thyroid related events, injection site reactions and neoplasms. A potential signal of an “increased lipase as an AE was reported by 11% in the insulin detemir + liraglutide group compared to the other groups (3.4% and 3.8%). In the response to the RSI it was clarified that this difference in frequency 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 1842 elevated serum lipase was not associated with increases in amylase or the observed events of pancreatitis. Also of note was the frequency of neoplasms—During the main study period (26W) 0%, 0.6% and 2.0% were observed in the insulin detemir+liraglutide+metformin, randomised and non-randomised liraglutide+metformin groups, respectively. 52 weeks safety data were submitted in response to the RSI in which it became apparent that, 7 new cases (4.3%, 6 of them were malignant) of neoplasms were identified in the insulin detemir + liraglutide + metformin group during the 26 W extension period. No additional neoplasms were identified in the randomised liraglutide + metformin group whereas two neoplasms (2.4%) were observed in the non-randomised liraglutide +metformin group. There was no apparent clustering in the types of neoplasm seen in any of the groups.

Based on theoretical concerns regarding the growth of cancer a question was raised in the RSI whether additional pharmacovigilance activities were needed to reflect the potential safety issue that basal insulin may promote liraglutide induced cancers and vice versa. Though the currently available data are limited (study duration too short to evaluate a potential tumour promoting effect), and therefore not convincing enough to answer this question, the differences in neoplasm frequency were noteworthy. Further pharmacovigilance activities have therefore been introduced to address this safety concern. There were no major hypoglycaemic episodes. Minor hypoglycaemic events occurred significantly more frequent in the insulin detemir + liraglutide group (8% of subjects) compared to the other treatment groups (liraglutide + metformin 1.3%, non-randomised liraglutide + metformin 3.8%). The frequency of minor hypoglycaemic events is not higher than that observed for insulin detemir in the original MAA

The cardiac safety data presented did not indicate that addition of insulin detemir to metformin + liraglutide 1.8mg give rise to any cardiac safety concern. Based on the original dossier for liraglutide cardiac events represent a possible concern for liraglutide and are 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. These initiatives are considered sufficient.

No deaths were observed during the main trial 1842. There were 11 serious adverse events (SAEs) reported in 8 patients (5.0%) in the liraglutide-metformin group, 14 SAEs in 9 patients (5.5%) in the insulin detemir + liraglutide + metformin group, 49 AEs in 39 patients (7.8%) in the non-randomised group, and 5 SAEs in 5 patients (3.0%) in the early withdrawal group. No clustering was evident for any of the treatment groups. Notably there was no SAE considered as probably or possibly related to study medication in the insulin detemir + liraglutide + metformin group.

With regards to discontinuations, no preponderance of discontinuations due to AEs in the insulin detemir + liraglutide + metformin group was seen.

**Conclusions on clinical safety**

Overall, based on the safety data from the 26 weeks extension study the overall safety profile observed with insulin detemir in combination with liraglutide seems to resemble that already known for liraglutide and insulin detemir. The outstanding issues are addressed in updated RMP.
2.2.3. Pharmacovigilance aspects

2.2.3.1. Detailed description of the Pharmacovigilance system

N/A

2.2.4. Risk management plan

The applicant has submitted a Risk Management Plan (RMP) version 10.0. The RMP is written in accordance with the current guidelines.
## Summary of the risk management plan

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Proposed Pharmacovigilance Activities</th>
<th>Proposed Risk Minimisation Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identified Risks</td>
<td>Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)</td>
<td>Addressed in the SmPC, Sections 4.4, 4.5, 4.7 and 4.8. Section 4.4 Special warnings and precautions for use: Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes. Concomitant illness, especially infections and feverish conditions, usually increases the patient’s insulin requirements. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in insulin dose. When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin. Section 4.5 Interaction with other medicinal products and other forms of interaction: Beta-blocking agents may mask the symptoms of hypoglycaemia. Alcohol may intensify or reduce the hypoglycaemic effect of insulin. Section 4.7 Effects on ability to drive and use machines: The patient’s ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances. Section 4.8 Undesirable effects: The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in</td>
</tr>
</tbody>
</table>

Assessment report  
EMA/903008/2011  
Page 34/43
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Proposed Pharmacovigilance Activities</th>
<th>Proposed Risk Minimisation Activities</th>
</tr>
</thead>
</table>
| Injection site reactions | Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs) | Addressed in the SmPC, Sections 4.4 and 4.8.  
*Section 4.4 Special warnings and precautions for use:*  
As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Levenir®.  
*Section 4.8 Undesirable effects:* Injection site reactions are seen more frequently during treatment with Levenir® than with human insulin products. These reactions include pain, redness, hives, inflammation, bruising, swelling and itching at the injection site. Most of the injection site reactions are minor and of a transitory nature, i.e. they normally disappear during continued treatment in a few days to a few weeks.  
Listed as common (≥1/100 to <1/10) adverse reactions. |
| Lipodystrophy    | Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs) | Addressed in the SmPC.  
*Section 4.8 Undesirable effects:* Lipodystrophy is reported as uncommon. It may occur at the injection site as a consequence of failure to rotate injection sites within an area.  
Listed as uncommon (≥1/1,000 to ≤1/100) adverse reaction. |
| Oedema           | Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs) | Addressed in the SmPC.  
*Section 4.8 Undesirable effects:* At the beginning of the insulin treatment, oedema may occur; these reactions are usually of transitory nature. Listed as uncommon (≥1/1,000 to ≤1/100) adverse reaction. |
| Allergic reactions | Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs and follow-up questions for allergic reactions) | Addressed in the SmPC.  
*Section 4.8 Undesirable effects:* Allergic reaction, potentially allergic reaction, urticaria, rash and eruptions are uncommon when Levenir® is used in basal-bolus regimen. However, when used in combination with oral antidiabetic medicinal products, three clinical studies have shown a frequency of common (2.2% of allergic reactions and potentially allergic reactions have been observed).  
Listed as uncommon adverse reaction. |
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Proposed Pharmacovigilance Activities</th>
<th>Proposed Risk Minimisation Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important Potential Risks</td>
<td></td>
<td>The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life threatening. Anaphylactic reactions are listed as very rare (&lt;1/10,000) adverse reactions</td>
</tr>
<tr>
<td>Cardiovascular &amp; cerebrovascular events</td>
<td>Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Antibody formation</td>
<td>Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs and follow-up questions for allergic reactions)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Microvascular complications of the eye</td>
<td>Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Medication errors</td>
<td>Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Potential anti-insulin antibody development in relation to NN729 process (allergic reactions and lack of efficacy)</td>
<td>Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs and follow-up questions for allergic reactions)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
| Potential risk of malignant neoplasms following combination treatment with insulin detemar + liraglutide + metformin | Single case reporting including targeted follow-up questionnaires Aggregated periodic reporting these cases will be described and evaluated in dedicated sections within the PSURs and ASRs/DSURs  
- Non-clinical study on the *in vitro* mitogenicity in various cell lines  
- Literature search on the mitogenic potency of insulin and insulin | Not applicable                                                                                                                                                        |
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Proposed Pharmacovigilance Activities</th>
<th>Proposed Risk Minimisation Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>analogues</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Non-clinical study on the combined effect of insulin detemir and liraglutide on cell growth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pharmacoepidemiological study using GPRD (Observational study into the prescribing of liraglutide in combination with insulin detemir in the GPRD, and the risk of cancer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• A feasibility report on 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</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Statistical analysis plan for the on-going cardiovascular outcome trial (EX2211-3748, LEADER™) will be provided.</td>
<td></td>
</tr>
</tbody>
</table>
The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

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

### 2.2.5. Changes to the Product Information

The following changes are proposed for the Product Information (deleted text strikethrough, new text in bold underlined):

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Proposed Pharmacovigilance Activities</th>
<th>Proposed Risk Minimisation Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-label use in children below the age of 2</td>
<td>Aggregated periodic reporting- these cases will be described and evaluated in dedicated sections within the PSURs and ASRs/DSURs</td>
<td>The SmPC will reflect that insulin detemir is indicated for patients above the age of 2 years.</td>
</tr>
<tr>
<td>Important Missing Information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td>Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)</td>
<td>Addressed in the SmPC, Sections 4.2 and 5.2 Special populations:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Section 4.2 Posology and method of administration:</strong> As with all insulin medicinal products, in elderly patients, glucose monitoring should be intensified and Levenir dosage adjusted on an individual basis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Section 5.2 Pharmacokinetic properties:</strong> There was no clinically relevant difference in pharmacokinetics of insulin detemir between elderly and young subjects.</td>
</tr>
<tr>
<td>Patients with renal or hepatic impairment</td>
<td>Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)</td>
<td>Addressed in the SmPC, Sections 4.2 and 5.2, Special populations:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Section 4.2 Posology and method of administration:</strong> As with all insulin medicinal products, in patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin detemir dosage adjusted on an individual basis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Section 5.2 Pharmacokinetic properties:</strong> There was no clinically relevant difference in pharmacokinetics of insulin detemir between subjects with renal or hepatic impairment and healthy subjects.</td>
</tr>
<tr>
<td>Children &lt;2 years</td>
<td>Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Patients with cardiac impairment</td>
<td>Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)</td>
<td>Not applicable.</td>
</tr>
</tbody>
</table>
4.2 Posology and method of administration

**Posology**

The potency of insulin analogues, including insulin detemir, is expressed in units (U), whereas the potency of insulin human is expressed in international units (IU). 1 unit (U) insulin detemir corresponds to 1 international unit (IU) of insulin human.

**Levemir can be used alone as the basal insulin or in combination with bolus insulin. It can also be used in combination with oral antidiabetic medicinal products or as add-on therapy to liraglutide treatment.**

In combination with oral antidiabetic medicinal products and as add-on to liraglutide it is recommended to use Levemir once daily, initially at a dose of 10 U or 0.1-0.2 U/kg. The dose of Levemir should be titrated based on individual patients’ needs.

5.1 Pharmacodynamic properties

An open-label randomised clinical trial in patients with type 2 diabetes not reaching target with oral anti-diabetic medicinal products was conducted. The trial started with a 12 week run-in period with liraglutide+metformin, where 61% reached an HbA1c <7%. The 39% of patients not achieving target were randomised to have Levemir once-daily added or continue on liraglutide+metformin for 52 weeks. Addition of Levemir provided a further reduction of HbA1c from 7.6% to 7.1% after 52 weeks. There were no major hypoglycaemic episodes. A major hypoglycaemic episode is defined as an episode where the subject was not able to treat him/herself and if glucagon or i.v. glucose was needed. See table 3.

**Table 3. Clinical trial data - Levemir add-on to liraglutide+metformin**

<table>
<thead>
<tr>
<th></th>
<th>Study week</th>
<th>Randomised Levemir + liraglutide ± metformin N = 160</th>
<th>Randomised Liraglutide + metformin N = 149</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in HbA1c from baseline (%)</td>
<td>0-26 weeks</td>
<td>-0.51</td>
<td>+0.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>0-52 weeks</td>
<td>-0.50</td>
<td>0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proportions of patients achieving HbA1c &lt;7% targets (%)</td>
<td>0-26 weeks</td>
<td>43.1</td>
<td>16.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>0-52 weeks</td>
<td>51.9</td>
<td>21.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in body weight from baseline (kg)</td>
<td>0-26 weeks</td>
<td>-0.16</td>
<td>-0.95</td>
<td>0.0283</td>
</tr>
<tr>
<td></td>
<td>0-52 weeks</td>
<td>-0.05</td>
<td>-1.02</td>
<td>0.0416</td>
</tr>
<tr>
<td>Minor hypoglycaemic episodes (per patient year)</td>
<td>0-26 weeks</td>
<td>0.224</td>
<td>0.019</td>
<td>0.0075</td>
</tr>
<tr>
<td></td>
<td>0-52 weeks</td>
<td>0.228</td>
<td>0.034</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

5.2 Pharmacokinetic properties

**Linearity**
Dose proportionality in serum concentrations (maximum concentration, extent of absorption) is observed after subcutaneous administration in the therapeutic dose range.

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

[...]

The Package Leaflet has been updated accordingly. In addition minor changes have been made throughout the Product Information.

### 2.3. Overall discussion and benefit-risk assessment

#### 2.3.1. Benefit

**Beneficial effects**

Two clinical studies were submitted for this proposed variation for Levemir.

The clinical pharmacology trial NN2211-3673 showed no PK/PD interactions between liraglutide and insulin detemir. 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. In addition, 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.

The phase 3 study NN2211-1842 evaluated the efficacy of insulin detemir as add-on to liraglutide 1.8mg and metformin in a 26 weeks randomised, open-label, two-armed, parallel-group, multicentre, multinational trial (proceeded by a 12 weeks run-in) with a 26-week extension. Type 2 diabetic patients insufficiently controlled on metformin (≥ 1500mg/day) or metformin + SU (½ maximum dose) were included in the 12 weeks run-in period during which, liraglutide was forced titrated to 1.8mg/day. The criterion for randomisation to the main 26 weeks treatment period (+/- insulin therapy) was an HbA1C ≥ 7.0%. Patients who did not fulfil the randomisation criterion at the end of the run-in period (i.e. HbA1c < 7.0%), continued treatment with liraglutide 1.8 mg + metformin in a non-randomised treatment arm.

Treatment with liraglutide + metformin + insulin detemir resulted in a statistically significant and clinically relevant decrease in HbA1c after 26 weeks treatment (**primary endpoint**) when compared to liraglutide + metformin (LSMean difference = -0.52% (95% CI: -0.68; -0.36), P<0.0001).

The superior efficacy of liraglutide + metformin + insulin detemir vs. liraglutide + metformin on the primary endpoint was supported by other endpoints reflecting glycaemic control: significantly more patients reached the target HbA1c < 7.0% (20.1% vs. 44.4%) and HbA1c<6.5% (19.4% vs. 7.4%) and also the changes in FPG and post-prandial PG reductions were significantly better.

The superior effect on glycaemic control of liraglutide + metformin + insulin detemir seemed to be at the expense of changes in body weight. The mean reductions in body weight from randomisation to week 26 were -0.16 and -0.95 kg for the triple and the dual therapy respectively, with an estimated body weight difference of 0.79 kg (95%CI: 0.08;1.49); p=0.0283) in favour of the liraglutide + metformin group. This difference however, is hardly of clinical relevance. Still, the data on body weight indicated that the liraglutide induced reductions in body weight observed during the 12 weeks run-in period were sustained during the 26 weeks study period.
Uncertainty in the knowledge about the beneficial effects

Potential differences in treatment effect on beta cell function could not be assessed in this study (HOMA-B and HOMA-IR) due to cross-reactivity between insulin detemir and the insulin assay.

2.3.2. Risks

Unfavourable effects

The overall pattern and frequencies of the most common adverse events in trial 1842 corresponds to what is already known for insulin detemir and liraglutide. During the run-in period the most common AEs were GI events, nausea, vomiting, diarrhoea, dyspepsia, and upper abdominal pain. These were markedly highest in those subjects withdrawing early (i.e. in the run-in period) and lowest in the triple therapy group. The data support the notion also reported in the original MAA for Liraglutide, that the incidence of nausea for most subjects is transient, with the highest number of subjects reporting nausea during the up-titration phase of liraglutide treatment. The most commonly reported adverse events during the 26-week main period were nasopharyngitis, diarrhoea and nausea, reported by 14.1%, 18.9% and 9.0% and 11.7%, 6.9% and 3.8% of subjects in the liraglutide + metformin + insulin detemir group and liraglutide + metformin group, respectively. The overall safety results from the 26 weeks extension study are in line with the safety data of the main period, with an overall comparable pattern between treatment groups. An exception however was the number of neoplasms. SAEs were comparable across treatment groups, with no clustering evident for any of the treatment groups.

There were no major hypoglycaemic episodes. During the 52 weeks trial minor hypoglycaemic events occurred significantly more frequent in the triple therapy group (0.23 events per subject years) compared to the other treatment groups (liraglutide + metformin 0.03 events per subject years, non-randomised liraglutide + metformin 0.12 events per subject years) The frequency of minor hypoglycaemic events is not higher than that observed for insulin detemir in the original MAA.

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

Uncertainty in the knowledge about the unfavourable effects

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 (liraglutide + metformin + insulin detemir).

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 liraglutide + metformin arm there were 5 malignant events in 4 patients. The percentage patients with malignant events was thus higher in the triple combination arm (3.1%) compared to the pooled liraglutide + metformin arms (0.76%).

There is the theoretical concern that basal insulin may promote potential liraglutide induced cancers and vice versa. The currently available data are limited (study duration too short to evaluate a potential tumour promoting effect), and are therefore not convinced enough to answer this question. It is acknowledged that insulin detemir was designed with a relative mitogenic potency of less or equal to human insulin (i.e. low binding affinity to the IGF-1 receptor, reserved balance between IGF-1 and IR binding and dissociation from the IR receptor similar to human insulin) and that clinical experience
with insulin detemir so far are not indicative of a tumour promoting effect. Nevertheless, the differences in neoplasm frequency are noteworthy.

Although, as mentioned above in the safety section, none of the 2 cases of pancreatitis occurred in the triple therapy group, the overall incidence of pancreas-related TEAEs was higher in the liraglutide + metformin + insulin detemir group (11.0%) when compared the randomised and non-randomised liraglutide + metformin groups (8.8%, 7.8%). 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 there was no signal that serum lipase increased over time in any of the treatment groups. Most importantly, in study 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.

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.

**Balance**

**Importance of favourable and unfavourable effects**

The favourable effects of insulin detemir on glycaemic control given as triple therapy in addition to metformin and liraglutide are clinically relevant. However, the provided data do not fully support the proposed up-dated wording of section 4.2 applied for "Levemir can be used alone as the basal insulin or in combination with bolus insulin. It can also be used in combination with oral antidiabetic medicines and glucagon–like peptide–1 (GLP–1) receptor agonists". No data has been provided supporting the use of liraglutide or other GLP-1 receptor agonists as add-on therapy to patients with an insufficient response to insulin. In addition, the data do not support the combination treatment of insulin with other GLP-1 receptor agonists. In the response to the RSI the Applicant has agreed to restrict the posology to “In combination with oral antidiabetic medicinal products and as add-on to liraglutide". This is considered acceptable.

When insulin detemir was added to therapy with metformin and liraglutide the overall safety profile did not change with one exception. The occurrence of malignant neoplasms was higher in the insulin detemir + liraglutide + metformin group vs. the two liraglutide + metformin groups.

**2.3.3. Benefit-risk balance**

Addition of insulin detemir to the combination of liraglutide and metformin offers clinically relevant improvement of glycaemic control in patients not sufficiently controlled on the dual therapy alone. The excess incidence of malignant neoplasms in the triple combination arm (liraglutide + metformin + insulin detemir) posed a major safety concern. Despite the fact that the neoplasms represent different locations and types/histologies, a general tumour promoting effect cannot be excluded. The MAH has 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 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 refers to the well-known association of type 2 diabetes and obesity with certain types of cancer. With respect to the association between insulin, 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.

Discussion on the benefit-risk assessment

The provided study supports the statistical and clinical relevance of superior glycaemic control when Levemir is added to metformin and liraglutide. Although, based on the excess number of malignancies in the triple treatment arm (liraglutide + metformin + Levemir), a general tumour promoting effect cannot be definitely excluded. Only large long-term trials with appropriate cancer endpoints would be able to answer this question.

Conclusions

The overall benefit-risk of Levemir in use as add-on therapy to liraglutide treatment is positive. The proposed update of the SmPC is endorsed.

3. Conclusion

On 22 September 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.