23 April 2015
EMA/CHMP/245829/2015 - adopted
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Levemir

International non-proprietary name: insulin detemir

Procedure No. EMEA/H/C/000528/II/0071

Marketing authorisation holder (MAH): Novo Nordisk A/S

Note

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

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List of abbreviations

AE	adverse event
AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CTR	clinical trial report
EASD	European Association for the Study of Diabetes
EMA	European Medicines Agency
EU	European Union
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated haemoglobin A1c
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IDeg	insulin degludec
IDet	insulin detemir
kg	kilogram
kg/m2	kilogram per meter squared
mg	milligram
mmol/L	millimole per litre
OAD	oral anti-diabetic drug
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
s.c.	subcutaneous(ly)
SmPC	Summary of Product Characteristics
SMPG	self-measured plasma glucose
SOC	system organ class
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

U	unit
UK	United Kingdom
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 7 January 2015 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name**
Levemir	insulin detemir

The following variation was requested:

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

Extension of indication to use levemir in combination with GLP-1 receptor agonists for the treatment of type 2 diabetes mellitus.
Consequently, the MAH proposed the update of sections 4.2, 4.5, and 5.1 of the SmPC. The Package Leaflet is updated in accordance.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0172/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0172/2014 was completed.

The PDCO issued an opinion on compliance for the PIP P/0172/2014.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jens Heisterberg Co-Rapporteur: Pieter de Graeff

Timetable	Actual dates
Rapporteur's preliminary assessment report circulated on:	19 March 2015
Rapporteur's updated assessment report circulated on:	20 April 2015
CHMP opinion:	23 April 2015

2. Scientific discussion

2.1. Introduction

Insulin detemir, registered as Levemir in the EU, is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

Insulin detemir is a long-acting insulin analogue used as a basal insulin. Novo Nordisk was granted marketing authorisation for insulin detemir in the European Union (EU) in 2004.

Type 2 diabetes mellitus (T2DM) is a progressive disease such that the majority of patients ultimately require insulin therapy. The inherent risks of hypoglycaemia and weight gain associated with insulin therapy act as barriers to the timely initiation and intensification of insulin therapy.

Consequently, a considerable number of patients experience suboptimal glycaemic control and fail to meet recommended glycosylated haemoglobin A_{1c} (HbA_{1c}) targets set to reduce the risk of long-term complications.

Glucagon-like peptide-1 (GLP-1) receptor agonists can, by allowing a decrease of insulin dose, reduce the risks of hypoglycaemia and weight gain inherent to insulin therapy and thereby enable a larger proportion of patients to achieve glycaemic targets. In the joint position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for treatment of T2DM, the combined use of a GLP-1 receptor agonist and a basal insulin is recommended as an option for third-line therapy once patients fail to achieve adequate glycaemic control on second-line therapy: metformin in combination with either another oral anti-diabetic drug (OAD), a GLP-1 receptor agonist or a basal insulin. The position statement underscores the importance of individualised treatment regimens, and the combined use of a basal insulin and a GLP-1 receptor agonist is one recommended option.

Basal insulins and GLP-1 receptor agonists act through different but complementary mechanisms. Basal insulins increase glucose disposal in peripheral tissues and suppress hepatic glucose production between meals and during sleep. GLP-1 receptor agonists increase insulin secretion and suppress glucagon secretion, both in a glucose-dependent manner. Combination therapy with a basal insulin and a GLP-1 receptor agonist takes advantage of the combined effects of both drugs on fasting glucose and the effect of GLP-1 receptor agonists on postprandial glycaemic control. When a GLP-1 receptor agonist is used with a basal insulin, then compared to insulin treatment alone, the requirement for basal insulin may be less, which can result in a lower risk of hypoglycaemia. Furthermore, the combined use of GLP-1 receptor agonists and basal insulins has been shown to have beneficial effects

on weight control compared to treatment with basal insulins alone due to the appetite and energy intake reducing effects of GLP-1 receptor agonists and the smaller dose of insulin required. These beneficial effects on glycaemic control, body weight and hypoglycaemia profile make the combined use of a GLP-1 receptor agonist and a basal insulin an attractive therapeutic option.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

Market data and marketing approvals for combinations of basal insulins with GLP-1 receptor agonists

Market data from 2012 from the EU [Germany, France and the United Kingdom (UK)] and United States (US), indicate that approximately 20% of all patients treated with a GLP-1 receptor agonist also use a basal insulin. A study performed by the Association of British Clinical Diabetologists (ABCD) in 2008 demonstrated that about 40% of patients treated with exenatide twice daily also used insulin, with the majority of patients adding exenatide on top of their existing insulin therapy, reflecting the fact that the combination of basal insulin and GLP-1 receptor agonists was already then used.

Based on clinical data, in recent years approvals have been granted in the EU for several GLP-1 receptor agonists to be used in combination with a basal insulin. Exenatide (Byetta) was approved as adjunctive therapy to basal insulin in 2012, and lixisenatide (Lyxumia) was approved in combination with basal insulin in 2013. In April 2014 liraglutide (Victoza) was approved for use in combination with basal insulin products. More recently, albiglutide and dulaglutide were also approved for the combined use with insulin in the EU.

As well, approvals have been granted in the EU for some basal insulin products to be used in combination with GLP-1 receptor agonists. Insulin degludec (Tresiba, [IDeg]) was approved in combination with GLP-1 receptor agonists in May 2014, and IDegLira (Xultophy), a fixed ratio combination product containing IDeg and liraglutide, received marketing authorisation from the European Medicines Agency (EMA) in September 2014.

The use of insulin detemir as add-on therapy to liraglutide treatment was approved in the EU in 2011.

Further information supporting the variation application

The present variation application was seeking approval for the use of insulin detemir in combination with GLP-1 receptor agonists for the treatment of T2DM. This application was supported by:

- new clinical trial results with insulin detemir;
- published studies in which insulin detemir, among other basal insulin products, was used in combination with lixisenatide; and
- extrapolation analogous to that which supported the recent approval of insulin degludec in combination with GLP-1 receptor agonists. The approval sought would achieve alignment of

information related to combination use in the Summary of Product Characteristics (SmPC) for insulin detemir with the information in the SmPCs of several GLP-1 receptor agonist products.

The 2011 approval of the use of insulin detemir as add-on therapy to liraglutide treatment was enabled by a previous variation application that sought the same broad approval as the present variation application: for insulin detemir to be used in combination with any GLP-1 receptor agonist. This previous variation application presented data from Trial 3673 and Trial 1842 to establish the efficacy and safety of insulin detemir in combination with GLP-1 receptor agonists in subjects with type 2 diabetes inadequately controlled by liraglutide in combination with metformin.

Trial 3673 evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) properties of insulin detemir and liraglutide when administered individually and when co-administered to insulin-naïve subjects with type 2 diabetes. The Trial 3673 results did not indicate any substantial PK or PD interaction between insulin detemir and liraglutide and indicated an additive PD effect of the two drugs.

Trial 1842 evaluated the efficacy and safety of adding insulin detemir for a period of 26 weeks to the treatment regimen of insulin-naïve subjects with type 2 diabetes who were inadequately controlled on liraglutide 1.8 mg + metformin. Treatment with insulin detemir + liraglutide 1.8 mg + metformin was superior to treatment with liraglutide 1.8 mg + metformin as measured by change from baseline to week 26 in HbA1c (estimated treatment difference of -0.52%) and fasting plasma glucose (FPG) (estimated treatment difference of -1.73 mmol/L). The safety profile of insulin detemir in Trial 1842 was consistent with the overall safety profile of combinations of insulin detemir with OADs.

However CHMP determined that the data provided in the previous variation application was not sufficient to justify approval for insulin detemir to be used in combination with any GLP-1 receptor agonist stating that 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, and that inaddition, the data did not support the combination treatment of insulin with other GLP-1 receptor agonists. Accordingly, the insulin detemir SmPC was updated to include only add-on therapy to liraglutide treatment at that time

Summary of new information in support of the present variation application

Concerning the order of initiation of basal insulin and GLP-1 receptor agonist

Trial 3917 was a phase 3b clinical trial designed to confirm the superiority of glycaemic control on liraglutide versus placebo after 26 weeks of treatment when added to pre-existing basal insulin analogue treatment (with or without concomitant metformin treatment) in subjects with T2DM not reaching HbA1c<7.0% (target). In Trial 3917, 33% of the subjects (147 out of 450 subjects) used insulin detemir as their basal insulin (the insulin detemir subgroup; the remainder used insulin glargine); the results from this subgroup are most relevant to the present variation application and are detailed here.

Therefore **this assessment report only focuses on a subgroup of subjects in Trial 3917.**

The efficacy and safety results from the insulin detemir subgroup of Trial 3917 demonstrate that liraglutide addition to pre-existing treatment with insulin detemir is efficacious and safe, as when the same two therapies are initiated in the reverse order, which was demonstrated in Trial 1842.

Additionally, data from the literature indicate that a net benefit results from the combination of a GLP-1 receptor agonist and a basal insulin, irrespective of which is the pre-existing treatment and which is added on.

Furthermore, the GLP-1 receptor agonists, liraglutide, exenatide and lixisenatide, that are approved in the EU in combination with basal insulin products, including insulin detemir, may be used without regard to order of initiation.

Concerning generalising to combination with any GLP-1 receptor agonist

Evidence of the efficacy and safety of insulin detemir in combination with GLP-1 receptor agonists beyond liraglutide comes from two published studies in which insulin detemir, among other basal insulin products, was used in combination with lixisenatide: GetGoal-L and GetGoal-L Asia. In GetGoal-L, lixisenatide was added for 24 weeks to existing therapy in T2DM patients inadequately controlled on basal insulin with or without metformin. Relative to placebo, lixisenatide addition decreased HbA1c, decreased post-prandial hyperglycaemia and decreased body weight. In this study 24 (7%) of the 328 lixisenatide-treated patients were on insulin detemir therapy. In GetGoal-L Asia, lixisenatide was added for 24 weeks to existing therapy in Asian T2DM patients inadequately controlled on basal insulin with or without sulfonylurea. Relative to placebo, lixisenatide addition decreased HbA1c, decreased post-prandial hyperglycaemia and decreased FPG. In this study, 83 (27%) of the 311 trial patients, 154 of whom received lixisenatide, were on insulin detemir therapy. In total there were two cases of unexplained severe hypoglycaemia and no cases of acute pancreatitis in the lixisenatide-treated patients. These data were included in the Assessment Report that supported the update of the lixisenatide SmPC to include information on combination use with basal insulin products.

Additionally, the use of the basal insulin, insulin degludec, in combination with GLP-1 receptor agonists was approved by the EMA based on extrapolation of efficacy and safety data obtained for insulin degludec in combination with liraglutide. Novo Nordisk suggests that similar extrapolation is reasonable for insulin detemir with regards to combination with GLP-1 receptor agonists other than liraglutide.

Furthermore, the exenatide SmPC discusses use with basal insulin, and the Assessment Report for exenatide specifically mentions insulin detemir: “Overall, the publications… describe exposure of more than 5000 subjects to exenatide in combination with short-acting and/or basal insulins, including (when specified) insulin glargine and insulin detemir.”

The proposed insulin detemir SmPC update would align information to physicians with the information already appearing in the SmPCs of several GLP-1 receptor agonist products regarding combination use.

Overall, the CHMP acknowledged that in the EU, all marketed GLP-1 receptor agonists have been approved in combination with a basal insulin. Thus, exenatide, lixisenatide and liraglutide have been approved as adjunctive therapy to basal insulin. Furthermore, insulin detemir is approved as add-on therapy to liraglutide. On the basis on clinical trial 3917, previous published studies with detemir and lixisinatide and extrapolation of the approved indication of insulin degludec in combination with GLP-1 agonist, the MAH is now seeking approval also for the use of insulin detemir in combination with GLP-1 receptor agonists for the treatment of T2DM. It is emphasised that the approval of insulin degludec in combination with GLP-1 agonists in general was granted on the basis of studies all evaluating the use of basal insulin (IDeg or IDet) in combination with liraglutide

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

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

2.3.2. Clinical pharmacology

No new relevant data has been submitted in this application, which was considered acceptable by the CHMP.

2.4. Clinical efficacy

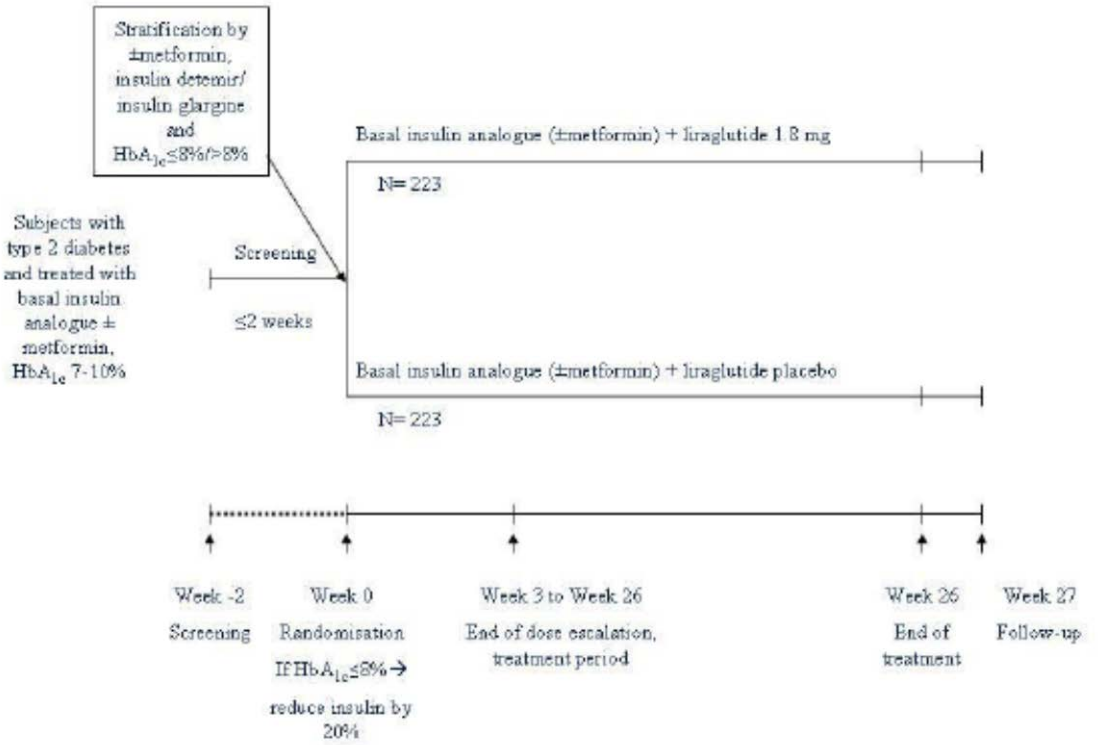
In this report the efficacy results from a subgroup of subjects in the phase 3b clinical trial NN2211-3917 (hereafter referred to as Trial 3917) is assessed. This trial was designed to confirm the superiority of glycaemic control on glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide (1.8 mg dose), versus placebo, randomised 1:1, after 26 weeks of treatment when added to pre-existing basal insulin analogue treatment (with or without concomitant metformin) in male and female subjects with type 2 diabetes mellitus (T2DM) not reaching glycosylated haemoglobin A_{1c} (HbA_{1c}) <7.0% (target). In this trial, 33% (147) of the subjects used insulin detemir as their basal insulin (the insulin detemir subgroup; the remainder used insulin glargine). As it is this insulin detemir subgroup that is most relevant to the variation application, "Use of insulin detemir in combination with GLP-1 Receptor Agonists", this assessment focuses on the efficacy results from the insulin detemir subgroup, and results from the overall trial population are not detailed here.

2.4.1. Main study

Trial design

Trial 3917 was a 26-week, randomised, double blind, placebo-controlled, parallel group, multi-centre, multi-national trial investigating the efficacy and safety of liraglutide in subjects with T2DM.

Subjects, including 147 subjects using insulin detemir (≥20 U/day), were randomised in a 1:1 manner to receive subcutaneous (s.c.) liraglutide 1.8 mg or placebo once daily in addition to their pre-trial basal insulin. Subjects initiated liraglutide treatment at 0.6 mg/day at randomization and increased the dose to 1.2 mg/day after one week, and further to 1.8 mg/day after two weeks; or they received placebo (liraglutide vehicle) analogously. The dose of liraglutide or placebo remained unchanged thereafter and until the end of the trial (Figure below). If subjects were treated with metformin at trial inclusion, they continued with metformin at a stable, pre-trial dose level, dosing frequency and formulation throughout the trial at the discretion of the investigator. Subjects with an HbA_{1c}>8.0% at screening continued their current basal insulin analogue treatment (insulin glargine or insulin detemir) at a stable, pre-trial dose level and dosing frequency throughout the trial unless they experienced hypoglycaemia or were at risk of hypoglycaemia. Subjects with an HbA_{1c}≤8.0% at screening reduced their insulin dose by 20% at randomisation. After reaching the steady-state of liraglutide 1.8 mg/placebo at end of week 3, insulin could be up-titrated to no higher than the screening dose level based on three pre-visit fasting self-measured plasma glucose (SMPG) values at the discretion of the investigator. Otherwise, the insulin dose was to be kept at a stable, pre-trial dose level and dosing frequency throughout the trial unless subjects experienced hypoglycaemia or were at risk of hypoglycaemia.



At the randomisation visit (week 0), subjects meeting all inclusion and none of the exclusion criteria were randomised in a 1:1 manner to one of two parallel treatment groups, either liraglutide or placebo. Randomisation was stratified based on screening HbA1c (≤8.0% versus >8.0%), metformin treatment and type of basal insulin analogue (insulin glargine versus insulin detemir). There were no pre-specified targets for the percentage of subjects with a baseline HbA1c≤8.0% versus >8.0% or metformin usage in either treatment group. However, subjects were randomised such that neither treatment group had <30% or >70% of one type of basal insulin analogue.

In summary, trial 3917 was a randomised, double blind, placebo-controlled, parallel group trial investigating the efficacy and safety of liraglutide in subjects with T2DM. The substudy of study 3917, encompassing 1/3 of the study population includes subjects on insulin detemir. Thus the study further supports the combined use of liraglutide and insulin detemir.

Methods

- **Study participants**

The trial comprised male and female subjects with T2DM, aged 18−80 years, with a body mass index (BMI) of 20−45 kg/m24 and with an HbA1c of 7−10% (all ranges/measurements inclusive). Subjects were to have been treated with stable basal insulin analogue dose ± stable metformin for at least 8 weeks prior to screening.

Only serious concomitant conditions (New York Heart Association [NYHA] class IV congestive heart failure [CHF], history of recent serious cardiac event, neoplasms, renal or hepatic impairment in accordance with the current liraglutide [Victoza] labelling, and pre-planned major surgery and similar events) which would interfere with trial schedule/procedures precluded subjects from entering into the trial.

- **Treatments**

Trial 3917 was 26 weeks in duration to ensure the full effect of treatment on the primary endpoint, change in HbA1c from baseline.

The maximum recommended daily dose of liraglutide (1.8 mg/day) was used. In the insulin detemir + liraglutide group, liraglutide was initiated with a starting dose of 0.6 mg/day, with subsequent weekly dose escalations of 0.6 mg/day in accordance with the approved dose escalation for liraglutide until the maintenance dose of 1.8 mg/day was reached. In the insulin detemir + placebo group, placebo (liraglutide vehicle) was dosed analogously.

The trial design included a placebo control group to show that liraglutide added-on to background basal insulin analogue with or without metformin was more effective than placebo in lowering glycaemic parameters.

Subjects were treated with a minimum stable basal insulin analogue dose of 20 U/day ± stable metformin ≥1500 mg/day for at least 8 weeks prior to screening.

- **Outcomes/endpoints**

The **primary endpoint** of Trial 3917 was the change in HbA1c from baseline to week 26. Blood samples for determination of HbA1c were drawn at screening, at randomisation (week 0) and after 4, 8, 12, 20 and 26 weeks.

Only secondary efficacy endpoints in Trial 3917 that are relevant to the variation application, are described below.

Supportive endpoints related to HbA1c included proportions of subjects achieving the American Diabetes Association (ADA) glycaemic target of HbA_{1c}<7.0% and the American Association of Clinical Endocrinologists (AACE) target of HbA_{1c}≤6.5% at end of trial. These subjects were designated 'responders'. Furthermore, a composite responder endpoint reflected responders with respect to HbA_{1c} targets who did not experience minor or severe treatment-emergent hypoglycaemic episodes.

- **Statistical methods**

In Trial 3917, the analysis sets were defined in accordance with ICH E9.5

- Full analysis set (FAS) – included all randomised subjects who received at least one dose of trial product (liraglutide or placebo) and who provided at least one post-baseline efficacy value. In exceptional cases, subjects or observations from the FAS may be eliminated. In such cases, the elimination is justified and documented. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle and subjects contributed to the evaluation "as randomised".
- Safety analysis set (SAS) – included all subjects who received at least one dose of the trial product. Subjects in the safety set contributed to the evaluation "as treated".

The primary endpoint (change in HbA1c from baseline to week 26) was analysed using a mixed model repeated measurements (MMRM) analysis of all data for changes in HbA1c from baseline to week 4, 8, 12, 20, and 26, with treatment, country and stratification groups as factors and baseline HbA1c as a covariate, all nested within week. An unstructured covariance matrix was used to describe the variability for the repeated measurements for a subject. The mean treatment difference at week 26 was estimated from this model, and a 95% confidence interval (CI) and the associated two-sided p-value were calculated. The FAS was used for this analysis.

The primary objective of the trial was to confirm superiority of liraglutide vs. placebo as add-on to the pre-existing basal insulin analogue therapy ± metformin. The test of superiority is a two-sided test of the null hypothesis of no difference between the two treatment groups with respect to change from baseline in HbA1c (%) after 26 weeks of treatment. The alternative hypothesis is that there is a difference between the two treatment groups. The superiority of liraglutide will be considered confirmed when the 95% CI for the estimated treatment difference (liraglutide minus placebo) in change from baseline in HbA1c (%) after 26 weeks of treatment lies entirely below 0%.

An analysis of covariance (ANCOVA) model with treatment, country and stratification groups as factors and baseline HbA1c as a covariate was fitted to the primary endpoint as a sensitivity analysis. The last observation carried forward (LOCF) method was used to impute missing values. The treatment difference at week 26 was estimated from this model and a 95% CI and the associated p-value were calculated. The FAS was used for this analysis.

The same MMRM analysis that was used for the primary endpoint was also used for most of the continuous secondary efficacy endpoints. The only change was with regard to the covariate, where the baseline value of the variable in question was used instead of baseline HbA1c.

Daily basal insulin dose was assumed to be log-normally distributed; consequently, the insulin dose data were log-transformed before being analysed. The log-transformed insulin dose data were analysed in an MMRM with treatment, country and stratification groups as factors and the log-transformed baseline basal insulin dose as a covariate, all nested within visit. A compound symmetry model for the covariance structure was used, since the model with an unstructured covariance matrix would not converge. The treatment difference after 26 weeks of treatment was estimated from this model, and a 95% CI was calculated. The estimated mean difference and the CI were back-transformed to the original scale; thus the mean difference on the log-scale transforms to an insulin dose ratio (liraglutide over placebo) on the original scale.

The dichotomous (responder) endpoints were analysed by a logistic regression model with treatment, country and stratification groups as factors and with HbA1c at baseline as a covariate. The treatment odds ratio was estimated from this model and a 95% CI and associated p-value were calculated. In addition, percentages were estimated for each treatment group from the estimated odds for treatment group as:

$$100 \times \left(estimated\ treatment\ odds \div (1 + estimated\ treatment\ odds)\right).$$

Where there were too few subjects in a stratum within a country, it may have been necessary to remove the country factor from the model. Similarly, if there were convergence issues due to few subjects in a stratum, it may have been necessary to exclude that stratum from the analysis.

In order to obtain consistency between the statistical analyses of the continuous endpoints and the dichotomous endpoints, missing values for the continuous assessments were imputed from the predicted values from the MMRM models using empirical best linear unbiased predictors; imputed values for the continuous endpoints were used in the analysis of corresponding dichotomous endpoints.

Treatment-emergent adverse events (TEAEs) were summarised descriptively. TEAE data were presented as the number of subjects with at least one event, the percentage of subjects with at least one event, the number of events, and the event rate [number of events per 1000 patient (subject) years of exposure]. In addition, the TEAEs were summarised by seriousness, severity, relation to trial product, withdrawal due to AEs and outcome. Summary tables by system organ class (SOC), high level group term (HLGT) and preferred term (PT) were prepared for all TEAEs and for PTs occurring in at least 5% of the subjects in any treatment arm.

The total number of treatment-emergent confirmed hypoglycaemic episodes during 26 weeks of treatment was presented descriptively as the number of subjects with at least one episode, the percentage of subjects with at least one episode, the number of episodes, and the episode rate [number of episodes per 100 patient (subject) years of exposure]. In addition, the total number of treatment-emergent hypoglycaemic episodes during the 26 weeks of treatment was analysed using a negative binomial regression model with a log link function and the logarithm of the time period in which the hypoglycaemic episodes were considered treatment-emergent as an offset. The model included treatment, country and stratification groups as factors and the baseline HbA_{1c} value as covariate. The treatment rate ratio was estimated from this model, and a 95% CI and associated p-value were calculated.

The following clinically relevant endpoints were analysed for the insulin detemir subgroup: change in HbA_{1c} after 26 weeks of treatment, HbA1c responder endpoints, change in FPG after 26 weeks of treatment, change in body weight after 26 weeks of treatment, daily basal insulin dose after 26 weeks of treatment and number of hypoglycaemic episodes. Furthermore, TEAE data for this subgroup were presented. Approximately one third of the subjects in the full Trial 3917 contributed with data to the analyses for the insulin detemir subgroup. The FAS and SAS were identical for the insulin detemir subgroup.

It was not possible to fit the exact same statistical model for hypoglycaemic episodes in the insulin detemir subgroup as the model used for the full trial population; the country factor had to be excluded from the model. Therefore, an extra sensitivity analysis in which the country factor was excluded from the MMRM model was added for change in HbA1c, change in FPG and change in body weight.

In addition, for the hypoglycaemic episodes and for the responder endpoints, the stratum “without metformin” was too small and had to be excluded from the analysis. This was in line with the analysis of the full trial population, where the stratum “insulin detemir without metformin” was removed from the analyses.

Overall, approximately one third of the subjects in the full Trial 3917 contributed with data to the analyses for the insulin detemir subgroup. The FAS and SAS were identical for the insulin detemir subgroup. It was not possible to fit the exact same statistical model for hypoglycaemic episodes in the insulin detemir subgroup as the model used for the full trial population; the country factor had to be excluded from the model. Therefore, an additional sensitivity analysis in which the country factor was excluded from the MMRM model was added for change in HbA_{1c}, change in FPG and change in body weight. This was considered to be acceptable by CHMP.

Results

- **Participant flow**

A total of 147 subjects using insulin detemir in Trial 3917 were randomised with 75 subjects in the insulin detemir + liraglutide group and 72 in the insulin detemir + placebo group. All randomised subjects were exposed to the trial product (liraglutide or placebo), and 124 subjects (84.4%) completed the trial: 69 subjects (92.0%) in the insulin detemir + liraglutide group and 55 subjects (76.4%) in the insulin detemir + placebo group (Table 2–2).

Table 2–2 Subject disposition of subjects using insulin detemir

	Liraglutide 1.8 mg N (%)	Placebo N (%)	Total N (%)
Randomised	75 (100.0)	72 (100.0)	147 (100.0)
Exposed	75 (100.0)	72 (100.0)	147 (100.0)
Completed	69 (92.0)	55 (76.4)	124 (84.4)
Withdrawn after randomisation	6 (8.0)	17 (23.6)	23 (15.6)
Adverse Event	3 (4.0)	0 (0.0)	3 (2.0)
Non-compliance with protocol	2 (2.7)	1 (1.4)	3 (2.0)
Withdrawal criteria [1]	1 (1.3)	16 (22.2)	17 (11.6)
Subject may withdraw at will any time	1 (1.3)	6 (8.3)	7 (4.8)
Safety concern or judged non-compliant	0 (0.0)	7 (9.7)	7 (4.8)
Unacceptable hyperglycaemia	0 (0.0)	3 (4.2)	3 (2.0)
Full analysis set	75 (100.0)	72 (100.0)	147 (100.0)
Safety analysis set	75 (100.0)	72 (100.0)	147 (100.0)

N: Number of subjects %: Percentages are based on randomised subjects
[1] Subjects can discontinue due to more than one withdrawal criteria

In the insulin detemir + liraglutide group, 6 subjects (8.0%) withdrew from the trial, of whom 3 subjects (4.0%) withdrew due to an adverse event, 2 subjects (2.7%) withdrew due to non-compliance with the protocol, and 1 subject (1.3%) withdrew at will.

In the insulin detemir + placebo group, 17 subjects (23.6%) withdrew from the trial: 1 subject (1.4%) withdrew due to non-compliance with the protocol and 16 subjects (22.2%) fulfilled withdrawal criteria. Three reasons for fulfilling withdrawal criteria were given: “safety concern or judged non-compliant” (7 subjects; 9.7%), “subject may withdraw at will at any time” (6 subjects; 8.3%) and “unacceptable hyperglycemia” (3 subjects; 4.2%).

- **Demographic and Baseline data**

Demographics and baseline characteristics of the insulin detemir subgroup subjects randomised in Trial 3917 are summarised in Table 2–1. The treatment groups were well-balanced with respect to demographics and baseline characteristics with a few differences that were not considered clinically important. Subjects treated with insulin detemir + liraglutide tended to be older than subjects treated with insulin detemir + placebo with mean ages of 61.7 and 57.6 years, respectively; however, their mean durations of diabetes were similar (12.0 versus 11.5 years). Mean baseline body weight was lower in the insulin detemir + liraglutide group (88.7 kg) than in the insulin detemir + placebo group (92.4 kg); however, baseline BMI was similar (31.9 versus 32.4 kg/m2). All subjects treated with insulin detemir + placebo took metformin, whereas 5.3% of subjects treated with insulin detemir + liraglutide did not. Although mean baseline FPG was slightly higher for the insulin detemir + liraglutide group than for the insulin detemir +placebo group (8.7 mmol/L versus 8.3 mmol/L), no difference in mean baseline HbA1c values between the two groups was observed (8.2% in both groups).

Table 2–1 Demographics and baseline characteristics of subjects using insulin detemir

	Liraglutide 1.8 mg	Placebo	Total
Number (N) of Subjects	75	72	147
Age (years) Mean (SD)	61.7 (8.7)	57.6 (12.1)	59.7 (10.7)
Age Group (N) (%)			
65-74	24 (32.0)	16 (22.2)	40 (27.2)
18-64	47 (62.7)	50 (69.4)	97 (66.0)
≥ 75	4 (5.3)	6 (8.3)	10 (6.8)
Duration of Diabetes (years) Mean (SD)	12.05 (7.17)	11.53 (6.36)	11.80 (6.77)
Sex (N) (%)			
Female	35 (46.7)	33 (45.8)	68 (46.3)
Male	40 (53.3)	39 (54.2)	79 (53.7)
Race (N) (%)			
White	65 (86.7)	66 (91.7)	131 (89.1)
Black or African American	2 (2.7)	1 (1.4)	3 (2.0)
Asian	7 (9.3)	4 (5.6)	11 (7.5)
American Indian or Alaska Native	1 (1.3)	1 (1.4)	2 (1.4)
Ethnicity (N) (%)			
Hispanic or Latino	17 (22.7)	14 (19.4)	31 (21.1)
Not Hispanic or Latino	58 (77.3)	58 (80.6)	116 (78.9)
Body Weight (kg) Mean (SD)	88.74 (19.401)	92.39 (21.055)	90.53 (20.242)
BMI (kg/m^2) Mean (SD)	31.9 (5.3)	32.4 (5.8)	32.1 (5.5)
BMI Group (N) (%)			
18.5-24.9	8 (10.7)	6 (8.3)	14 (9.5)
25.0-29.9	19 (25.3)	24 (33.3)	43 (29.3)
30.0-34.9	22 (29.3)	16 (22.2)	38 (25.9)
35.0-39.9	21 (28.0)	18 (25.0)	39 (26.5)
≥ 40.0	5 (6.7)	8 (11.1)	13 (8.8)
HbA1c (%) Mean (SD)	8.19 (0.806)	8.24 (0.898)	8.22 (0.850)
HbA1c Stratification (N) (%)			
HbA1c ≤ 8.0%	37 (49.3)	37 (51.4)	74 (50.3)
HbA1c > 8.0%	38 (50.7)	35 (48.6)	73 (49.7)
FPG (mmol/L) Mean (SD)	8.74 (2.981)	8.33 (2.983)	8.54 (2.979)
Metformin strata (N) (%)			
No	4 (5.3)	0 (0.0)	4 (2.7)
Yes	71 (94.7)	72 (100.0)	143 (97.3)

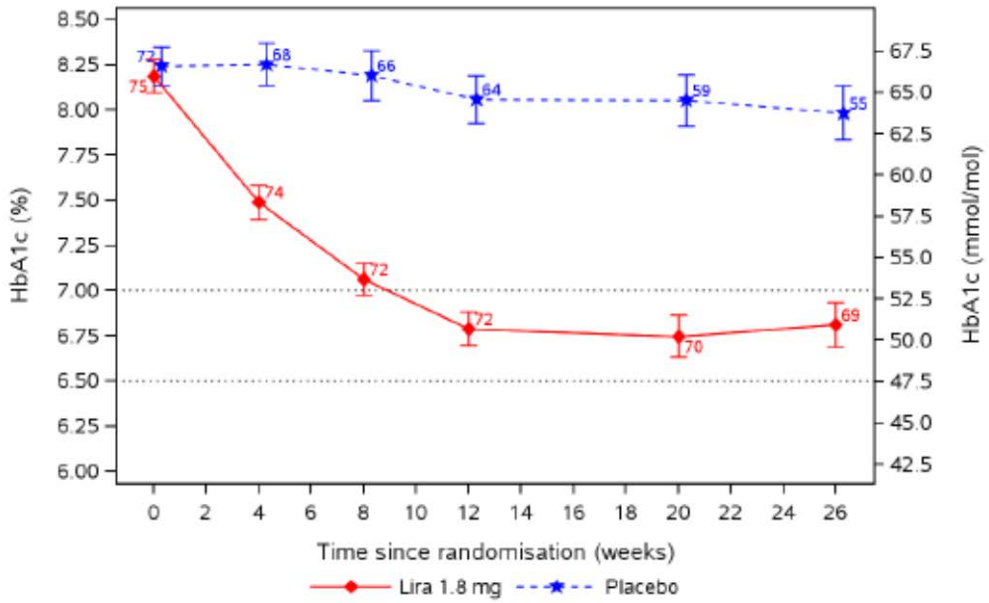
N: Number of subjects %: Percentages are based on N SD: Standard deviation
BMI: Body mass index HbA1c: Glycosylated haemoglobin A1c FPG: Fasting plasma glucose

Overall, the treatment groups were well-balanced with respect to demographics and baseline characteristics

- **Outcomes and estimation**

Primary endpoint – change in HbA1c

For the insulin detemir subgroup of Trial 3917, the efficacy of liraglutide versus placebo addition was evident from the change in observed HbA1c mean values over the 26-week trial period (Figure 2–1).



Observed means +/- standard error. Number corresponds to number of subjects contributing with data.

Figure 2–1 Observed mean HbA_{1c} by treatment week for subjects using insulin detemir

The estimated mean HbA1c values after 26 weeks of treatment were 6.93% and 8.24% for the insulin detemir + liraglutide and insulin detemir + placebo treatment groups, respectively. The estimated mean changes in HbA1c from baseline to week 26 were −1.24% for subjects treated with insulin detemir + liraglutide and +0.07% for subjects treated with insulin detemir + placebo; the estimated treatment difference was −1.31% [−1.67; −0.94]95% CI (p<0.0001) (Table 2–3). Treatment with insulin detemir + liraglutide was therefore superior to insulin detemir + placebo in terms of change in HbA1c from baseline to week 26, and this conclusion is supported by sensitivity analysis based on LOCF.

Table 2–3 HbA_{1c} (%) after 26 weeks of treatment for subjects using insulin detemir

	FAS	N	Estimate	95% CI	P-value
Estimated means					
Lira 1.8 mg	75	74	6.93		
Placebo	72	69	8.24		
Estimated means, change from baseline					
Lira 1.8 mg	75	74	-1.24		
Placebo	72	69	0.07		
Estimated treatment difference					
Lira 1.8 mg - Placebo			-1.31	[-1.67 ; -0.94]	<.0001

FAS: Full analysis set N: Number of subjects contributing to analysis CI: Confidence interval

Secondary efficacy endpoints and insulin detemir dose

Proportion of subjects achieving HbA_{1c} targets

There were three responder secondary endpoints evaluated for the insulin detemir subgroup: HbA_{1c}<7.0% (ADA target); HbA_{1c}≤6.5% (AACE target); and HbA_{1c}<7.0% with no minor or severe hypoglycaemic episodes.

HbA_{1c}<7.0% (ADA target)

The estimated percentages of responders achieving HbA_{1c}<7.0% at week 26 were 59.1% in the insulin detemir + liraglutide group and 10.3% in the insulin detemir + placebo group. The estimated odds ratio was 12.60 [4.93; 32.18]95% CI (p<0.0001). Statistically significantly more subjects treated with insulin detemir + liraglutide reached target compared to subjects treated with insulin detemir + placebo.

HbA_{1c}≤6.5% (AACE target)

The estimated percentages of responders achieving HbA_{1c} ≤6.5% at week 26 were 45.2% in the insulin detemir + liraglutide group and 1.0% in the insulin detemir + placebo group. The estimated odds ratio was 83.81 [10.47; 670.9]95% CI (p<0.0001). Statistically significantly more subjects treated with insulin detemir + liraglutide reached target compared to subjects treated with insulin detemir + placebo.

HbA_{1c}<7.0% with no minor or severe hypoglycaemic episodes

The estimated percentages of responders achieving HbA1c<7.0% who had no minor or severe hypoglycaemic episodes were 48.9% in the insulin detemir + liraglutide group and 9.9% in the insulin detemir + placebo group. The estimated odds ratio was 8.75 [3.48; 21.98]95% CI (p<0.0001).

Statistically significantly more subjects treated with insulin detemir + liraglutide reached target with no minor or severe hypoglycaemic episodes compared to subjects treated with insulin detemir + placebo.

Fasting plasma glucose

The estimated mean changes in FPG after 26 weeks of treatment were −1.13 mmol/L and −0.20 mmol/L for the insulin detemir + liraglutide and insulin detemir + placebo treatment groups, respectively, resulting in an estimated treatment difference of −0.93 mmol/L [−1.65; −0.21]95% CI (p=0.0122). The estimated mean FPG values after 26 weeks of treatment were 7.20 mmol/L and 8.13 mmol/L, respectively, for the insulin detemir + liraglutide and insulin detemir + placebo treatment groups.

Body weight

The estimated mean changes in body weight from baseline to week 26 were −3.47 kg and −0.43 kg in the insulin detemir + liraglutide and insulin detemir + placebo groups, respectively. The estimated treatment difference was −3.04 kg [−4.38; −1.70]95% CI (p<0.0001).

Insulin detemir dose

A reduction in initial insulin dose for subjects with baseline $HbA_{1c} \leq 8.0\%$ (requested per protocol) was reflected in initial decreases in all measures of observed insulin dose in both treatment groups. Following subsequent dose titration, numerically lower values of all insulin dose measures were observed for the subjects treated with insulin detemir + liraglutide than for the subjects treated with insulin detemir + placebo. This is exemplified by Figure 2–2, which plots observed insulin detemir daily dose per kg body weight ratio to baseline by treatment week.

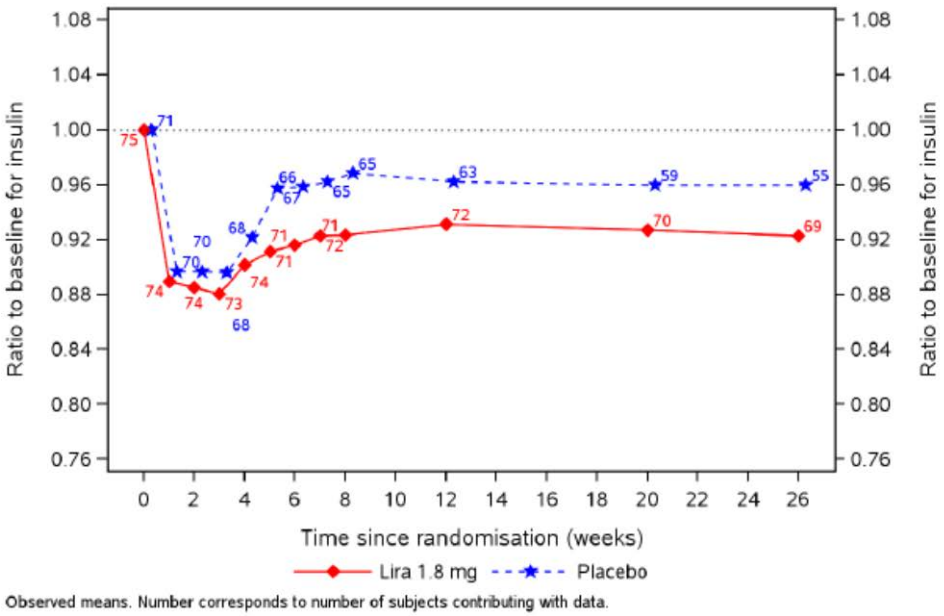


Figure 2–2 Observed insulin daily dose per kg body weight ratio to baseline by treatment week for subjects using insulin detemir

The estimated mean insulin detemir daily doses per kg body weight (U/kg) after 26 weeks of treatment were 0.43 U/kg and 0.45 U/kg in the insulin detemir + liraglutide and insulin detemir + placebo groups, respectively. The corresponding ratios to baseline were 0.92 and 0.98, and the estimated treatment ratio was 0.94 [0.90; 0.98]95% CI (p=0.0041).

Summary of efficacy results

The decrease in HbA1c after 26 weeks of treatment was greater with insulin detemir + liraglutide 1.8 mg than with insulin detemir + placebo, and superiority was thus confirmed for insulin detemir + liraglutide 1.8 mg compared with insulin detemir + placebo. In addition, secondary supportive analyses showed a greater percentage of responders in the insulin detemir + liraglutide group than in the insulin detemir + placebo group for every responder endpoint: $HbA_{1c} < 7.0\%$ (ADA target), $HbA_{1c} \leq 6.5\%$ (AACE target) and $HbA_{1c} < 7.0\%$ with no minor or severe hypoglycaemic episodes.

The decrease in FPG from baseline to week 26 was greater with insulin detemir + liraglutide treatment than with insulin detemir + placebo, as was weight loss. These results were associated with a lower daily dose of insulin detemir in subjects treated with liraglutide compared to those treated with placebo. Moreover, these results for the insulin detemir subgroup are consistent with the results from the full trial population of Trial 3917 and are statistically significant, despite the smaller data set.

Overall, the decrease in HbA_{1c} after 26 weeks was greater with liraglutide than with placebo, and superiority was confirmed. Secondary supportive analyses were in accordance with that and also a lower daily dose of insulin detemir was observed in subjects treated with liraglutide compared to placebo. The results are in line with the results from the full trial population of Trial 3917.

2.4.2. Discussion on clinical efficacy

Efficacy results were provided from a subgroup of subjects in the phase 3b clinical trial 3917 designed to confirm the superiority of liraglutide (1.8 mg dose), versus placebo, added to basal insulin. In the present variation application focus was on the subgroup of subjects (147) using insulin detemir as their basal insulin. The sub-study showed that liraglutide was superior for achieving glycaemic control versus placebo, i.e. greater HbA1c reduction, greater proportions of subjects achieving responder endpoints related to HbA_{1c} targets and hypoglycaemic episodes after 26 weeks of treatment. These benefits were achieved using a lower daily dose of insulin and the results were consistent with the results from the full trial population.

2.4.3. Conclusions on the clinical efficacy

The data showed that addition of liraglutide in subjects suboptimally controlled on insulin detemir is superior for achieving glycaemic control compared to placebo.

2.5. Clinical safety

Introduction

This safety section focuses on a subgroup of subjects in Trial 3917, a phase 3b clinical trial designed to confirm the superiority of liraglutide versus placebo for glycaemic control after 26 weeks of treatment when added to pre-existing basal insulin analogue treatment (with or without concomitant metformin treatment) in subjects with T2DM not reaching HbA_{1c}<7.0% (target). In Trial 3917, 33% of the subjects used insulin detemir as their basal insulin (the insulin detemir subgroup). This safety section focuses on the results from the insulin detemir subgroup, as the results from this subgroup are most relevant to the present variation application.

Patient exposure

Exposure data for the insulin detemir subgroup of Trial 3917 (75 subjects in the insulin detemir + liraglutide group and 72 in the insulin detemir + placebo group) are summarised in the table below. For these subjects, over the 26-week trial period, the total exposure for the insulin detemir + liraglutide group was 35.5 years, and for the insulin detemir + placebo group, total exposure was 31.6 years. The mean exposures for the two groups were 0.47 and 0.44 years, respectively, which were similar to the mean exposures for the full Trial 3917 populations

1: Exposure - summary - safety analysis set

	Lira 1.8 mg	Placebo	Total
Number of Subjects	75	72	147
Total Exposure, yrs	35.46	31.56	67.01
Exposure (yrs)			
N	75	72	147
Mean (SD)	0.47 (0.10)	0.44 (0.13)	0.46 (0.11)
Median	0.50	0.50	0.50
Geometric mean (CV)	0.44 (0.61)	0.40 (0.53)	0.42 (0.57)
Min ; Max	0.01 ; 0.53	0.07 ; 0.58	0.01 ; 0.58

Mean exposures for the insulin detemir + liraglutide and insulin detemir + placebo groups were 0.47 and 0.44 years, respectively, which were similar to the mean exposures for the full Trial 3917 populations.

Adverse events

Definition, handling, coding and adjudication of events

Only TEAEs were used for the tabulation and analysis of AEs. In Trial 3917, a TEAE, other than a hypoglycaemic episode, was defined as an event that had an onset date (or increase in severity) on or after the first day of exposure to randomised treatment and no later than seven days after the last day of randomised treatment. A hypoglycaemic episode was defined as treatment-emergent if the onset of the episode was on or after the first day of exposure to randomised treatment and no later than the day after last administration of trial product.

An external, independent events adjudication committee (EAC) was established for Trial 3917 to perform adjudication, standardisation and assessment of events of neoplasms and events of thyroid disease requiring thyroidectomy, including partial thyroidectomy (e.g., lobectomy, partial lobectomy) in an independent and blinded manner for randomised subjects. All neoplasm events, irrespective of malignancy stage, were adjudicated.

Analysis of adverse events

Adverse events overall

TEAEs were more common in the insulin detemir + liraglutide group (69.3% of subjects, 4202 events per 1000 PYE) than in the insulin detemir + placebo group (51.4% of subjects, 3866 events per 1000 PYE).

12: Treatment emergent adverse events - summary - safety analysis set

	Lira 1.8 mg N	(%)	E	R	Placebo N	(%)	E	R	Total N	(%)	E	R
Number of Subjects	75				72				147			
Events	52	(69.3)	149	4202	37	(51.4)	122	3866	89	(60.5)	271	4044
Serious												
Yes	5	(6.7)	9	254	0	(0.0)	0	0	5	(3.4)	9	134
No	50	(66.7)	140	3948	37	(51.4)	122	3866	87	(59.2)	262	3910
Severity												
Severe	4	(5.3)	7	197	1	(1.4)	1	32	5	(3.4)	8	119
Moderate	23	(30.7)	30	846	18	(25.0)	40	1268	41	(27.9)	70	1045
Mild	40	(53.3)	112	3159	31	(43.1)	81	2567	71	(48.3)	193	2880
Related to Investigational Product												
Probably	19	(25.3)	29	818	1	(1.4)	1	32	20	(13.6)	30	448
Possibly	13	(17.3)	26	733	7	(9.7)	13	412	20	(13.6)	39	582
Unlikely	39	(52.0)	90	2538	35	(48.6)	106	3359	74	(50.3)	196	2925
Missing	4	(5.3)	4	113	2	(2.8)	2	63	6	(4.1)	6	90
Related to Device												
No	52	(69.3)	145	4089	37	(51.4)	120	3803	89	(60.5)	265	3954
Missing	4	(5.3)	4	113	2	(2.8)	2	63	6	(4.1)	6	90

N= Number of Subjects
%= Percentage of Subjects
E= Number of Events
R= Event Rate per 1000 Patient Years of Exposure
A treatment emergent adverse event is defined as an event that has onset date on or after the first day of treatment and no later than seven days after the last day of treatment or increases in severity during treatment.
Related to investigational product: assessed by the investigator

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Treatment emergent adverse events - summary - safety analysis set

	Lira 1.8 mg N	(%)	E	R	Placebo N	(%)	E	R	Total N	(%)	E	R
Outcome												
Recovered	49	(65.3)	126	3554	33	(45.8)	102	3232	82	(55.8)	228	3402
Recovering	2	(2.7)	2	56	3	(4.2)	3	95	5	(3.4)	5	75
Recovered with Sequelae	1	(1.3)	1	28	0	(0.0)	0	0	1	(0.7)	1	15
Not Recovered	13	(17.3)	17	479	9	(12.5)	15	475	22	(15.0)	32	478
Unknown	2	(2.7)	3	85	2	(2.8)	2	63	4	(2.7)	5	75

TEAEs by system organ class (SOC), high level group term (HLGT) and preferred term (PT) are presented below:

14: Treatment emergent adverse events by system organ class, high level group term and preferred term - summary - safety analysis set

	Lira 1.8 mg				Placebo				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	75				72				147			
Number of adverse events	52	(69.3)	149	4202	37	(51.4)	122	3866	89	(60.5)	271	4044
Gastrointestinal disorders	28	(37.3)	44	1241	15	(20.8)	21	665	43	(29.3)	65	970
Gastrointestinal signs and symptoms	25	(33.3)	35	987	8	(11.1)	11	349	33	(22.4)	46	686
Nausea	22	(29.3)	28	790	5	(6.9)	6	190	27	(18.4)	34	507
Vomiting	2	(2.7)	2	56	2	(2.8)	3	95	4	(2.7)	5	75
Dyspepsia	1	(1.3)	1	28	1	(1.4)	1	32	2	(1.4)	2	30
Eructation	2	(2.7)	2	56					2	(1.4)	2	30
Abdominal distension	1	(1.3)	1	28					1	(0.7)	1	15
Abdominal pain					1	(1.4)	1	32	1	(0.7)	1	15
Flatulence	1	(1.3)	1	28					1	(0.7)	1	15
Gastrointestinal motility and defaecation conditions	5	(6.7)	7	197	3	(4.2)	3	95	8	(5.4)	10	149
Diarrhoea	5	(6.7)	7	197	2	(2.8)	2	63	7	(4.8)	9	134
Constipation					1	(1.4)	1	32	1	(0.7)	1	15
Dental and gingival conditions	1	(1.3)	1	28	3	(4.2)	5	158	4	(2.7)	6	90
Toothache	1	(1.3)	1	28	1	(1.4)	3	95	2	(1.4)	4	60
Dental caries					1	(1.4)	1	32	1	(0.7)	1	15
Gingival disorder					1	(1.4)	1	32	1	(0.7)	1	15

N= Number of subjects
%= Percentage of subjects
E= Number of Events
R= Event Rate per 1000 Exposure Years
A treatment emergent adverse event is defined as an event that has onset date on or after the first day of treatment and no later than seven days after the last day of treatment or increases in severity during treatment.

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05DEC2014:14:55:54 - tsum_events_tpl_t030_v01.sas/t_te_ae_sum_pt_sas.txt

Treatment emergent adverse events by system organ class, high level group term and preferred term - summary - safety analysis set

	Lira 1.8 mg				Placebo				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Abdominal hernias and other abdominal wall conditions					1	(1.4)	1	32	1	(0.7)	1	15
Inguinal hernia					1	(1.4)	1	32	1	(0.7)	1	15
Gastrointestinal stenosis and obstruction	1	(1.3)	1	28					1	(0.7)	1	15
Ileus	1	(1.3)	1	28					1	(0.7)	1	15
Oral soft tissue conditions					1	(1.4)	1	32	1	(0.7)	1	15
Oral disorder					1	(1.4)	1	32	1	(0.7)	1	15

Common adverse events

TEAEs occurring in at least 5% of subjects (4 or more subjects) in either treatment group at the PT level are presented in Table 2–1. The most common TEAEs in the insulin detemir + liraglutide group were gastrointestinal disorders (37.3% of subjects, 1241 events per 1000 PYE), infections and infestations (24.0% of subjects, 959 events per 1000 PYE), and musculoskeletal and connective tissue disorders (16.0% of subjects, 395 events per 1000 PYE). The most commonly reported TEAEs in the insulin detemir + placebo group were infections and infestations (27.8% of subjects, 951 events per 1000 PYE), gastrointestinal disorders (20.8% of subjects, 665 events per 1000 PYE), and musculoskeletal and connective tissue disorders (16.7% of subjects, 444 events per 1000 PYE).

Thus, the greatest difference in TEAEs between the two treatment groups was observed for gastrointestinal disorders, particularly nausea, which was experienced by 29.3% of subjects in the insulin detemir + liraglutide group (790 events per 1000 PYE) and 6.9% of subjects in the insulin detemir + placebo group (190 events per 1000 PYE).

Table 2–1 Treatment-emergent adverse events occurring in at least 5% of subjects using insulin detemir

	Liraglutide 1.8 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	75				72			
Number of adverse events	52	(69.3)	149	4202	37	(51.4)	122	3866
Gastrointestinal disorders	28	(37.3)	44	1241	15	(20.8)	21	665
Gastrointestinal signs and symptoms	25	(33.3)	35	987	8	(11.1)	11	349
Nausea	22	(29.3)	28	790	5	(6.9)	6	190
Gastrointestinal motility and defaecation conditions	5	(6.7)	7	197	3	(4.2)	3	95
Diarrhoea	5	(6.7)	7	197	2	(2.8)	2	63
Infections and infestations	18	(24.0)	34	959	20	(27.8)	30	951
Infections - pathogen unspecified	16	(21.3)	25	705	12	(16.7)	18	570
Nasopharyngitis	5	(6.7)	7	197	3	(4.2)	3	95
Viral infectious disorders	5	(6.7)	6	169	7	(9.7)	8	254
Influenza	1	(1.3)	2	56	6	(8.3)	7	222
Musculoskeletal and connective tissue disorders	12	(16.0)	14	395	12	(16.7)	14	444
Musculoskeletal and connective tissue disorders NEC	10	(13.3)	11	310	7	(9.7)	8	254
Back pain	8	(10.7)	9	254	4	(5.6)	4	127
Nervous system disorders	6	(8.0)	6	169	9	(12.5)	14	444
Headaches	1	(1.3)	1	28	7	(9.7)	9	285
Headache	1	(1.3)	1	28	7	(9.7)	9	285
Investigations	7	(9.3)	10	282	3	(4.2)	3	95
Gastrointestinal investigations	4	(5.3)	5	141	1	(1.4)	1	32
Lipase increased	4	(5.3)	4	113	1	(1.4)	1	32

N: Number of subjects %: Percentage of subjects
E: Number of Events R: Event Rate per 1000 exposure years

TEAEs within the SOC gastrointestinal disorders (e.g., nausea) are known adverse drug reactions of liraglutide and other drugs in the GLP-1 receptor agonist class. The higher rates of gastrointestinal disorders reported in the insulin detemir + liraglutide group were therefore expected and were consistent with previous results from the liraglutide clinical programme.

Hypoglycaemic episodes

Hypoglycaemic episodes were categorised according to the American Diabetes Association (ADA) classification3 .

Because in normal physiology hypoglycaemic symptoms occur at plasma glucose (PG) levels of approximately 3.1 mmol/L (56mg/dL), Novo Nordisk has defined an additional term, “minor hypoglycaemia”, which is either an episode with symptoms consistent with hypoglycaemia with confirmation by plasma glucose <3.1 mmol/L (56 mg/dL) or whole blood glucose <2.8 mmol/L (50 mg/dL), and which is handled by the subject him/herself; or is any asymptomatic plasma glucose value <3.1 mmol/L (56 mg/dL) or whole blood glucose value <2.8 mmol/L (50 mg/dL).

Confirmed hypoglycaemic episodes comprised minor hypoglycaemic episodes (MAH classification) and severe hypoglycaemic episodes (ADA classification). Hypoglycaemic episodes were classified as nocturnal if the time of onset was between 00:01 and 05:59, both inclusive.

There were no severe hypoglycaemic episodes in either group. Treatment-emergent confirmed hypoglycaemic episodes were observed for a similar percentage of subjects and at similar rates for subjects in the insulin detemir + liraglutide group (13.3%, 68 episodes per 100 PYE) compared to subjects in the insulin detemir + placebo group (12.5%, 67 episodes per 100 PYE) (Table 2–2). No statistically significant difference was seen between treatment groups in the rates of confirmed hypoglycaemic episodes; the estimated treatment rate ratio for insulin detemir + liraglutide versus insulin detemir + placebo was 1.19 with a 95% confidence interval (CI) of [0.34; 4.14]95% CI

(p=0.7846). The rate of overall hypoglycaemia according to ADA classification was numerically higher for the insulin detemir + liraglutide group (415 episodes per 100 PYE with 40.0% of subjects experiencing an episode) compared to the insulin detemir + placebo group (377 episodes per 100 PYE with 29.2% of subjects experiencing an episode) (Table 2–2). Compared to subjects in the insulin detemir + placebo group, subjects in the insulin detemir + liraglutide group experienced numerically higher rates of nocturnal confirmed hypoglycaemia (31 episodes per 100 PYE versus 16 episodes per 100 PYE, respectively, with 6.7% versus 2.8% of subjects experiencing an episode) and nocturnal overall hypoglycaemia (107 episodes per 100 PYE versus 51 episodes per 100 PYE, respectively, with 13.3% versus 9.7% of subjects experiencing an episode).

Table 2–2 Treatment-emergent hypoglycaemic episodes by classification for subjects using insulin detemir

	Liraglutide 1.8 mg			Placebo			Total		
	N	(%)	E R	N	(%)	E R	N	(%)	E R
Number of Subjects	75			72			147		
Confirmed	10	(13.3)	24 68	9	(12.5)	21 67	19	(12.9)	45 67
Minor	10	(13.3)	24 68	9	(12.5)	21 67	19	(12.9)	45 67
ADA classification	30	(40.0)	147 415	21	(29.2)	119 377	51	(34.7)	266 397
Severe	0	(0.0)	0 0	0	(0.0)	0 0	0	(0.0)	0 0
Documented sympt.	21	(28.0)	86 243	16	(22.2)	81 257	37	(25.2)	167 249
Asymptomatic	16	(21.3)	56 158	10	(13.9)	34 108	26	(17.7)	90 134
Probable sympt.	0	(0.0)	0 0	2	(2.8)	2 6	2	(1.4)	2 3
Relative	3	(4.0)	5 14	1	(1.4)	2 6	4	(2.7)	7 10
ADA unclassified	1	(1.3)	1 3	1	(1.4)	2 6	2	(1.4)	3 4

N: Number of subjects %: Percentage of subjects with the event (episode)
E: Number of Events (episodes) R: Event (episode) Rate per 100 patient years of exposure

Hypoglycaemia results may be related to insulin detemir dose, and the addition of liraglutide led to a decrease in insulin detemir dose.

Summary of adverse events

The greatest difference in TEAEs between the two treatment groups was observed for the SOC gastrointestinal disorders. Subjects in the insulin detemir + liraglutide group experienced more gastrointestinal disorders, particularly nausea, than subjects in the insulin detemir + placebo group. Gastrointestinal disorders are known adverse drug reactions of liraglutide and other drugs in the GLP-1 receptor agonist class, and they were expected in the insulin detemir + liraglutide group based on previous results from the liraglutide clinical programme.

There were no TEAEs with a fatal outcome during this trial. Two post-treatment deaths were reported, both of which were judged unlikely to be related to trial product.

Five subjects in the insulin detemir + liraglutide group were reported to have experienced TESAEs; all of which were classified by the investigator as unlikely to be related to the trial product and no two of which were of the same type.

Three subjects treated with insulin detemir + liraglutide withdrew from this trial due to TEAEs. Two of these subjects withdrew due to TEAEs that were classified as having a possible or probable relation to the trial product and were all non-serious.

There were no severe hypoglycaemic episodes in either treatment group. Treatment-emergent confirmed hypoglycaemic episodes were observed for a similar percentage of subjects and at similar rates in the two treatment groups. The rates of overall hypoglycaemia according to ADA classification, nocturnal confirmed hypoglycaemia and nocturnal overall hypoglycaemia were numerically higher for

the insulin detemir + liraglutide group; however, the percentage of subjects reaching HbA1c target without hypoglycaemia was also greater for the insulin detemir + liraglutide group.

These safety results for the insulin detemir subgroup are consistent with the safety results from the full trial population of Trial 3917, and the overall safety profile of liraglutide 1.8 mg added to insulin detemir is consistent with the individual overall safety profiles of liraglutide and insulin detemir as described in their respective Summaries of Product Characteristics.

Overall, as expected the greatest difference in TEAEs between the treatment groups was observed for the SOC gastrointestinal disorders. Subjects in the insulin detemir + liraglutide group experienced more gastrointestinal disorders, particularly nausea, than subjects in the insulin detemir + placebo group. There were no severe hypoglycaemic episodes in either treatment group. TEAE confirmed hypoglycaemic episodes were observed for a similar percentage of subjects and at similar rates in the two treatment groups. The rates of overall hypoglycaemia nocturnal confirmed hypoglycaemia and nocturnal overall hypoglycaemia were numerically higher for the insulin detemir + liraglutide group; however, the percentage of subjects reaching HbA_{1c} target without hypoglycaemia was also greater for the insulin detemir + liraglutide group.

These safety results for the insulin detemir subgroup are consistent with the safety results from the full trial population of Trial 3917 and the overall safety profile of liraglutide 1.8 mg added to insulin detemir is consistent with the individual overall safety profiles of liraglutide and insulin detemir as described in their respective SmPCs.

Serious adverse events and deaths

Deaths

There were no TEAEs with a fatal outcome during this trial. Two post-treatment deaths were reported:

A 67-year-old female treated with liraglutide for 123 days prior to withdrawal due to SAEs (pneumonia, fracture of the right ankle joint and foot after a fall, and non-ST elevation myocardial infarction) that were not considered related to the trial product. The subject had a previous history of breast cancer for which she was treated with radiotherapy. At screening, the subject was taking insulin detemir and metformin, and had an $HbA_{1c} \leq 8.0\%$. Approximately 2 months after withdrawal from the trial, the subject was admitted to the hospital with epigastric pain, and an abdominal computed tomography (CT) scan confirmed a pancreatic tumour with liver and lymph node metastases. The tumour was assumed to be malignant as no biopsy was performed; the tumour was inoperable and no additional treatment was initiated. The subject was also treated for Escherichia coli septicaemia during this hospitalisation. The subject was discharged 11 days after hospitalisation and died approximately 1 week later after a short period of palliative care. The investigator deemed both the pancreatic tumour and E. coli septicaemia as unlikely to be related to the trial product (liraglutide).

A 64-year-old male treated with placebo for 36 days and was then withdrawn due to safety/non-compliance. The subject was diagnosed with T2DM in 2003 and had renal impairment since 2012. There was no known personal or family history of cancer. At screening, the subject was taking insulin detemir and metformin, and had an $HbA_{1c} > 8.0\%$. At the end of trial visit, no complaints were reported. Two months after the end of trial visit, the subject was hospitalised due to the progression of left-sided paresis and dysarthria over the past 3 months. Two days later, a magnetic resonance imaging (MRI) confirmed a brain tumour in the right parietal lobe. No biopsy was performed, and no treatment options were available. The subject died approximately 7 weeks after diagnosis. The investigator deemed this event as unlikely to be related to the trial product (placebo).

Other serious adverse events

Five subjects in the insulin detemir + liraglutide group were reported to have experienced 9 treatment-emergent serious adverse event (TESAEs); no subjects in the insulin detemir + placebo group were reported to have experienced any TESAE (please see table below). All TESAEs were classified by the investigator as unlikely to be related to the trial product. All subjects recovered from all TESAEs by the end of the trial. The 9 TESAEs included 3 severe TESAEs, all of which occurred in one subject: pneumonia, fall and acute myocardial infarction; see also information about the 67-year-old female above. There were 3 moderate and 3 mild TEAEs. No 2 TESAEs were of the same type.

Overall, there were no TEAEs with a fatal outcome during this trial. Two post-treatment deaths were reported.

Laboratory findings

No specific analysis was made for the subgroup of subjects using insulin detemir as their basal insulin.

Safety in special populations

For the subgroup of subjects in Trial 3917 using insulin detemir as their basal insulin, no further subanalysis was performed.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to AES

A total of 6 TEAEs reported in 3 subjects treated with insulin detemir + liraglutide and no TEAEs in subjects treated with insulin detemir + placebo led to withdrawal from this trial. Of the 6 TEAEs leading to withdrawal, 3 were classified by the investigator as unlikely to be related to the trial product: pneumonia, fall and acute myocardial infarction; all serious and severe). Two TEAEs were classified by the investigator as having a possible relation to the trial product: non-serious, increased lipase classified as mild in severity and non-serious, severe headache. One TEAE was deemed probably related to the trial product: non-serious, severe nausea. The subjects recovered from all of these TEAEs by the end of the trial.

Three subjects in the insulin detemir + placebo group were withdrawn due to the distinct withdrawal criterion “unacceptable hyperglycaemia”.

17: Treatment emergent adverse events leading to withdrawal - safety analysis set

Centre	Treatment	Subject ID/ Age/Sex/ BMI	AE No.	Diag (Y/N)/ Link	System organ class/ High level group term/ Preferred term/ Reported term	Onset date/ Outcome	Study day/ Duration (days)	Serious (Y/N)/ Severity	AE related to technical complaints	Relation/ Action taken
211	Lira 1.8 mg	[redacted] 57.5/M/ 30.3	1	N	Investigations/ Gastrointestinal investigations/ Lipase increased/ Lipase increased: shown on Lab Report, Report Date of 20-DEC-2012. (Received at lab 19-DEC-2012, Collected and sent to lab 18-DEC-2012)	18DEC2012/ RECOVERED	83/ 38	N/ MILD	N	POSSIBLE/ PRODUCT WITHDRAWN PERMANENTLY
212	Lira 1.8 mg	[redacted] 55.0/F/ 25.6	1	N	Gastrointestinal disorders/ Gastrointestinal signs and symptoms/ Nausea/ Nausea	23MAR2013/ RECOVERED	2/ 4	N/ SEVERE	N	PROBABLE/ PRODUCT WITHDRAWN PERMANENTLY
			2	N	Nervous system disorders/ Headaches/ Headache/ Headache	25MAR2013/ RECOVERED	4/ 2	N/ SEVERE	N	POSSIBLE/ PRODUCT WITHDRAWN PERMANENTLY

Age: Age (years), AE No.: Adverse event number, M: Male, F: Female, BMI: Body mass index (kg/m^2)
Diag: Is the event a diagnosis that covers previous signs/symptoms?
Link: Link to symptom, Y: Yes, N: No, Relation: Relationship to trial product
A treatment emergent adverse event is defined as an event that has an onset date on or after the first day of treatment and no later than seven days after the last day of treatment or increases in severity during treatment.

Treatment emergent adverse events leading to withdrawal - safety analysis set

Centre	Treatment	Subject ID/ Age/Sex/ BMI	AE No.	Diag (Y/N)/ Link	System organ class/ High level group term/ Preferred term/ Reported term	Onset date/ Outcome	Study day/ Duration (days)	Serious (Y/N)/ Severity	AE related to technical complaints	Relation/ Action taken
212	Placebo	[redacted] 46.6/F/ 42.7	5	N	Metabolism and nutrition disorders/ Glucose metabolism disorders (incl diabetes mellitus)/ Hyperglycaemia/ Hyperglycemia	02MAY2013/ NOT RECOVERED	135/	N/ MODERATE	N	UNLIKELY/ PRODUCT WITHDRAWN PERMANENTLY
572	Lira 1.8 mg	[redacted] 66.7/F/ 31.6	1	N	Infections and infestations/ Infections - pathogen unspecified/ Pneumonia/ pneumonia	14MAR2013/ RECOVERED	123/ 22	Y/ SEVERE	N	UNLIKELY/ PRODUCT WITHDRAWN PERMANENTLY
			2	N	Injury, poisoning and procedural complications/ Injuries NEC/ Fall/ fracture of right ankle joint and foot after a fall	14MAR2013/ RECOVERED	123/ 56	Y/ SEVERE	N	UNLIKELY/ PRODUCT WITHDRAWN PERMANENTLY

Age: Age (years), AE No.: Adverse event number, M: Male, F: Female, BMI: Body mass index (kg/m^2)
Diag: Is the event a diagnosis that covers previous signs/symptoms?
Link: Link to symptom, Y: Yes, N: No, Relation: Relationship to trial product
A treatment emergent adverse event is defined as an event that has an onset date on or after the first day of treatment and no later than seven days after the last day of treatment or increases in severity during treatment.

Overall, a total of 6 TEAEs reported in 3 subjects treated with insulin detemir + liraglutide and no TEAEs in subjects treated with insulin detemir + placebo led to withdrawal from this trial

Post marketing experience

The post-marketing safety data for liraglutide and insulin detemir that is received by the MAH are made available in periodic safety update reports (PSURs)/periodic benefit risk evaluation reports (PBRERs) according to the regulatory requirements.

2.5.1. Discussion on clinical safety

As expected well-known AEs occurring with liraglutide treatment were common in the insulin detemir + liraglutide group and considered to be related to trial product. There were no TEAEs that were considered to be related to trial product, and there were no unexpected patterns of TEAEs of any kind. Hypoglycaemia rates was similar or higher in the insulin detemir + liraglutide group compared to the insulin detemir + placebo group. In line with that and as emphasised previously, the percentage of subjects reaching HbA1c target without hypoglycaemia was also greater for the insulin detemir + liraglutide group. No severe hypoglycaemic episodes were reported. Importantly, safety results for this sub-study are consistent with the safety results from the full trial population of Trial 3917.

2.5.2. Conclusions on clinical safety

The safety profile of liraglutide added to insulin detemir is consistent with the individual overall safety profiles of liraglutide and insulin detemir.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

Analysis of data from Trial 3917 did not lead to a significant change to the established benefit risk profile of insulin detemir, and the MAH confirms that the current approved risk management plan remains unchanged and applicable.

The current risk management plan was found to be acceptable.

2.7. Update of the Product information

SmPC

Section 4.2 Posology and method of administration

Posology

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

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 and/or GLP-1 receptor agonists.~~or as add-on therapy to liraglutide treatment.~~

~~In combination with oral antidiabetic medicinal products and as add-on to liraglutide~~ When Levemir is used in combination with oral antidiabetic medicinal products or when added to GLP-1 receptor agonists it is recommended to use Levemir once daily, initially at a dose of 10 units or 0.1-0.2 units/kg. The dose of Levemir should be titrated based on the individual patient's needs.

When a GLP-1 receptor agonist is added to Levemir, it is recommended to reduce the dose of Levemir by 20% to minimise the risk of hypoglycaemia. Subsequently, dosage should be adjusted individually.

Sections 4.5 and 5.1

These sections have also been updated (see SmPC text).

Package leaflet

The Package leaflet has been updated accordingly.

3. Benefit-Risk Balance

Benefits

The purpose of the current variations application is to propose a labelling update for the use of insulin detemir in combination with glucagon-like peptide 1 (GLP-1) receptor agonists.

Beneficial effects

In study 3917 a subgroup of 1/3 of the study population was using insulin detemir as their basal insulin and it was shown that addition of liraglutide was superior for achieving glycaemic control compared to placebo and the benefits were achieved using a lower daily dose of insulin and weight loss. Further supporting the variation application are data from previous published studies with insulin detemir and lixisenatide and extrapolation from the approved indication of insulin degludec in combination with GLP-1 agonists.

Uncertainty in the knowledge about the beneficial effects

The clinical trials included with this variation application evaluate the use of detemir in combination with liraglutide. No data on the use of insulin detemir in combination with other GLP-1 agonists, e.g. exenatide or lixisenatide, has been submitted.

Risks

Unfavourable effects

The safety profile of liraglutide added to insulin detemir was consistent with the well-known individual overall safety profiles of liraglutide and insulin detemir.

Uncertainty in the knowledge about the unfavourable effects

There are no new uncertainties or safety concerns evoked in relation to the combination therapy.

Benefit-risk balance

Importance of favourable and unfavourable effects

The addition of liraglutide to insulin detemir treatment has been shown to result in clinically relevant reduction of HbA_{1c}. This reduction was achieved at a relatively low risk of hypoglycaemia and using a lower daily dose of insulin as well as weight loss. These effects are all considered of benefit in a T2DM population in need of intensified treatment. The safety data provided does not indicate any changes in the safety profiles for detemir or liraglutide when administered in combination. The adverse events known to occur with liraglutide predominated the adverse event reporting. These events are well known and are considered manageable.

Benefit-risk balance

Discussion on the benefit-risk balance

In the EU all GLP-1 receptor agonists authorised at the time of this report have been approved for the use in combination with a basal insulin. Thus, exenatide, lixisenatide,liraglutide, albiglutide and dulaglutide have been approved as adjunctive therapy to (basal) insulin. The MAH was seeking approval for the use of detemir in combination with any GLP-1 agonist. The submitted new study further supports the combined use of liraglutide and insulin detemir, which was already approved as add-on therapy to liraglutide in the SmPC of Detemir. The study in itself alone does not fully support the combined use with other GLP-1 agonists. However, as argued by the MAH the use of insulin detemir with other GLP-1 agonists is supported by published studies in which insulin detemir, among other basal insulin products, was used in combination with lixisenatide. Furthermore it is emphasized that the approval of insulin degludec in combination with GLP-1 agonists was based on extrapolation of data on the use of basal (degludec or detemir) in combination only with liraglutide. It is therefore accepted that the data obtained with detemir and liraglutide, together with the other information provided, can be extrapolated to sufficiently support the use of detemir in combination with GLP-1 receptor agonists in general.

Conclusion

The benefit risk balance for the use of insulin detemir (Levemir) in combination with GLP-1 receptor agonists is considered positive.

4. Recommendations

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

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

Extension of indication to use levemir in combination with GLP-1 receptor agonists for the treatment of type 2 diabetes mellitus.
Consequently, the MAH proposed the update of sections 4.2, 4.5 and 5.1 of the SmPC. The Package Leaflet is updated in accordance.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.