

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Levemir. For information on changes after approval please refer to module 8.**

### 1 Introduction

Insulin detemir, the active ingredient in Levemir, is an insulin analogue with a prolonged duration of action, and is produced by recombinant DNA technology using a genetically modified strain of *Saccharomyces cerevisiae*. In order to obtain a long-acting insulin product, the amino acid threonine in position B30 of the human insulin molecule has been omitted and myristic fatty acid has been attached to the  $\epsilon$ -amino group of amino acid lysine B29.

The goal of insulin treatment is to mimic the physiologic pattern of insulin secretion, which under normal conditions consist of a basal secretion and meal related short peaks. The most commonly used insulin regimen is the so-called basal-bolus regimen in which basal insulin requirements are provided by one or two injections of intermediate- or long-acting insulin and mealtime requirements are provided by meal related injections of short acting soluble human insulin/insulin analogues. It is generally accepted that the basal-bolus regimen offers the best glycaemic control, reducing the risk for complications resulting from diabetes such as retinopathy, nephropathy and neuropathy.

Levemir is indicated for use in patients with type 1 or type 2 diabetes mellitus, used as basal insulin in combination with pre-meal bolus injections with short-acting insulin. Levemir should be administered subcutaneously once or twice daily and should be adjusted individually, depending on patients' needs.

### 2 Quality aspects

#### Composition

The finished product is a solution for subcutaneous injection containing 100 U/ml (2400 nmol) insulin detemir. The excipients are mannitol, phenol, metacresol, zinc acetate, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections. The pH is 7.4. The product does not contain ingredients of animal or human origin.

The presentations are Levemir Penfill, Levemir FlexPen and Levemir Innolet, containing 1, 5 or 10 cartridges of 3 ml. The container is made of glass (type I) with a bromobutyl rubber closure shaped as a plunger and closed with a bromobutyl/polyisoprene rubber closure.

#### Drug substance

Insulin detemir (molecular mass 5916.9 Da) appears as a white to whitish crystalline powder, which is soluble in water. The chemical name of insulin detemir is Lys<sup>B29</sup> (N<sup>ε</sup>- tetradecanoyl)des(B30) insulin human. Insulin detemir is produced by recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) as the host organism. The manufacturing process for insulin detemir is identical to the applicant's licensed insulins until the purification step.

In insulin detemir the amino acid threonine in position B30 of the human insulin molecule has been omitted and myristic fatty acid has been attached to the  $\epsilon$ -amino group of amino acid lysine B29 by an acylation reaction.

The purpose of the molecular changes in insulin detemir is to achieve a high affinity for human albumin as a way of protracting insulin's biological effect thereby obtaining a long acting soluble insulin product. The biological activity can be determined *in-vitro* by measuring the insulin detemir-dose-dependent take-up of <sup>3</sup>H-glucose by murine adipocytes.

#### *Development genetics and cell bank system*

Insulin detemir is produced using a genetically modified strain of *Saccharomyces cerevisiae*. The plasmid is constructed based on the yeast 2 $\mu$  plasmid. The applicant has presented the complete DNA sequence of the plasmid. The sequencing presented is assembled from published sequences and in-house sequence determinations as relevant. The gene has also been fully characterised from isolated

plasmids from long-term production scale fermentation and cell bank (Original Mother Culture (OMC)).

The stability of the production strain was characterised by the sequencing of the insulin precursor gene of isolated plasmids from the long-term production scale fermentation (end of production) and the cell bank (Original Mother Culture (OMC)). Furthermore, plasmid stability is monitored as an in-process control during fermentation. Segregational stability is also routinely monitored by the in-process controls for insulin precursor positive phenotype in samples from production fermentations.

The cell bank system consists of Original Mother Culture (OMC), New Mother Culture (NMC), MCB and WCB.

### ***Production and purification***

The manufacturing process and the different intermediates of insulin detemir in the process are summarised below. The initial stages of production, i.e. the fermentation and recovery steps, are common to both the currently licensed (unmodified) human insulins and insulin detemir.

The batch numbering system is described in detail for the fermentation, the recovery and the purification/modification stages. The insulin precursor is produced and drawn continuously. In the recovery stage, the continuous process changes into a batch process.

**Fermentation and harvesting.** Agar medium is inoculated with yeast cells from a WCB vial. Subsequently, the yeast is transferred to the seed fermenter. When vigorous growth has developed, this culture is transferred aseptically to the main fermenter. The insulin precursor is concentrated by cation exchange chromatography followed by 2 crystallisation steps. The crystallised product is stored at -18°C until further processing.

**Downstream modification and purification.** The insulin human precursor (Insulin B1-B29-*Ala-Ala-Lys*-Insulin A1-A21) is passed through a reactor with immobilised enzyme.

This is followed by chromatographic steps to reduce product related impurities.

The myristoyl group ( $\text{CH}_3(\text{CH}_2)_{12}\text{CO}-$ ) is introduced by acylation onto the  $\epsilon$ -amino group on the side chain of lysine in position B29 of the DesB30-insulin whereby insulin detemir is formed.

The acylation is followed by chromatographic steps and precipitation.

Finally the active substance is crystallised and dried. The manufacturing and purification process has been sufficiently validated. Adequate in-process controls are in place to monitor manufacturing consistency and quality of the product. Column performance (purification capacity, separation, carry-over of proteins and viruses) is adequately monitored according to determined quality criteria with adequate alert limits.

### ***Manufacturing process development***

During early development insulin detemir was produced from a dedicated insulin detemir precursor. The insulin detemir precursor was expressed and secreted from yeast strain during the fermentation process, as a single chained structure with disulphide bridges. This process was used for the production of the active substance for early toxicity studies and early Phase I and II clinical trials.

As drug development progressed a new and more specific acylation method was developed. Consequently, a production strategy was adopted, in which the insulin human precursor could be used as the starting material.

#### **Insulin B1-B29-*Ala-Ala-Lys*-Insulin A1-A21**

This process was used for the production of the active substance for pre-clinical (long-term toxicity and reproduction studies), Phase I, Phase II and Phase III clinical trials and is the intended production process.

The comparison of active substance has confirmed that the structural and physico-chemical properties of active substance from the two processes are identical.

### ***Characterisation and specifications of the active substance***

The structure of insulin detemir has been elucidated through different analyses. One primary reference batch has been fully structurally and physico-chemically characterised. A secondary reference material as a working standard has also been produced. The content of insulin detemir in active substance and finished product is measured by RP-HPLC. The biological activity of insulin detemir is determined using an *in vitro* cell based effector assay known as the Free Fat Cell assay (FFC). The samples are measured against an insulin detemir reference material.

Two product-related substances have been identified in the insulin detemir active substance: the A21-desamido form and the B3-desamido form. The biological activities of these substances have been determined, and as product related substances they are included in the determination of assay value by HPLC.

The process-related impurities originate from the host organism *Saccharomyces cerevisiae* during fermentation and from the chemical modification steps. The testing of a number of impurities is discontinued based on a sufficiently large number of tested batches, which is considered acceptable. Adequate documentation has been presented to demonstrate the removal of the process-related impurities.

Insulin detemir product-related impurities are generated as by-products in the fermentation of the insulin human precursor by yeast and in the chemical modification steps.

Taken together, the impurities are either controlled in process testing or by specification testing of the active substance in an adequate manner. Alternatively adequate justification is provided. Consistency of impurity levels between pilot scale and production scale has been demonstrated.

In general, the specifications adequately control the quality of the active substance and are based on release test data from 20 pilot scale batches and 4 production scale batches as well as stability data from 3 batches followed for 24 months.

All methods for release testing of insulin detemir active substance according to the specification given above have been established in the relevant quality control (QC) laboratories and validated according to ICH guidelines.

### ***Stability of the active ingredient***

Stability studies have been performed at long-term conditions and at accelerated conditions on three pilot-scale and first three commercial-scale batches. The stability study on the first three commercial-scale batches is furthermore followed at 25°C.

Presently 24 months data for three pilot scale batches and 3 months data for the first three production scale batches are available. All results from the stability study were within the proposed specification during 24 months of storage. The stability studies on the pilot batches and the first three production batches are on-going to 60 months.

Stress testing and photostability testing has been performed. Photostability studies revealed that the degradation of insulin detemir increases when exposed to light. Therefore, the active substance should be protected from light.

Based on the results from the reported studies, a shelf life of 24 months is proposed for insulin detemir active substance stored at low temperature, protected from light.

### **Other ingredients**

Mannitol is used to modify tonicity, sodium chloride as a chemical stabilizer, disodium phosphate dihydrate as a pH buffering agent, zinc (as zinc acetate) as a physical stabilizer and phenol and metacresol as preservatives

The excipients used all comply with Ph.Eur, except for metacresol which complies with USP and a Novo Nordisk monograph.

## **Product development and finished product**

Three formulations of finished product were used in clinical trials. Early clinical trials - Phase I and Phase II- were carried out with formulation A. Formulation B was used in later Phase I and Phase II trials, as well as early phase III trials. Formulation C was used in late Phase I and Phase III trials and is the formulation intended for marketing.

The concentration of active substance was increased from 600 nmol/ml (formulation A) to 1200 nmol/ml (formulation B) and finally 2400 nmol/ml (formulation C) as clinical trials in human subjects with diabetes revealed a higher molar requirement of insulin detemir compared to human insulin to obtain the same glucose lowering effect.

All cartridge components (glass, plunger and stopper) meet the Ph.Eur. requirements. Severe long-term stability/compatibility studies show compatibility of primary container closure components with the insulin detemir product. An analytical study and a toxicity study did not give concern regarding the safety of the level of leachables. Furthermore, the primary container closure system is similar to other insulin human products.

The function and the dose accuracy of Levemir FlexPen and Levemir InnoLet have been tested with three different doses of insulin detemir 100 U/ml. The two devices fulfilled the dose accuracy tolerance limits defined in ISO 11608.

The facilities for production/packaging and quality control of the finished product are all located in Denmark. The manufacturing of the finished product is performed in accordance with cGMP and all equipment in contact with the filtered (0.22 µm) solution is sterilised by autoclave or dry heat steriliser. Furthermore, cartridges, caps and pistons are sterilised by validated processes.

Insulin detemir 100 U/ml is manufactured by mixing two aqueous solutions: solution (I) is a solution with neutral pH containing all excipients except zinc. Solution (II) is a weak alkaline solution containing insulin detemir and zinc acetate.

This bulk solution is then filtered (0.22 µm) into a stainless steel filling tank. Finally, the formulated bulk is filled into the final container in a class A environment. The process validation included four consecutive batches. The manufacturing process together with IPC has been adequately described and validation data are presented. The results of the specification analyses show that the manufacturing process used is capable of consistently producing Levemir 100 U/ml batches in production scale of the required quality.

### ***Specifications of the finished product***

Three major degradation products have been identified as product related substances. Of these only, B3-desamido insulin detemir is formed in significant amounts during storage at recommended conditions (0.9% after 18 months at 2-8°C).

### ***TSE and viral safety***

Three components in the storage medium for the WCB are from bovine origin, i.e. peptone, beef extract and pepticase. Peptone is also used in the propagation of the MCB. For the beef extract and peptone, EDQM Certificates of suitability are presented. The pepticase has been produced from bovine milk sourced from USA, Australia or New Zealand, fit for human consumption. In the production of pepticase, two secondary raw materials of animal origin are used; these are bovine derived lactose and a material of porcine origin.

Two additional raw materials of bovine origin, amicase and lactose are used in the manufacture of the enzyme *Achromobacter lyticus* protease (ALP). Both are produced from bovine milk from healthy animals and are considered acceptable.

Validation studies on virus removal/inactivation have not been performed on the basis that viruses are unable to replicate in the yeast cell line. Furthermore, the production processes for all materials contain steps that are considered virus inactivating (high temperature treatment (all materials) to high pH treatment (peptone)).

### **Stability of the Product**

The stability programme for the finished product involved a total of 6 studies; 18 months stability data at long-term conditions ( $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ ), twelve months data from accelerated conditions ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ) and three months at severe conditions ( $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ) have been submitted. The stability studies on the batches stored at  $5^{\circ}\text{C}$  are currently on-going.

Only minor changes are observed at  $5^{\circ}\text{C}$ , e.g. very small decrease in drug content and a slight or no increase in degradation products and high molecular weight proteins (HMWP). However, data from elevated temperatures  $25^{\circ}\text{C}$  and  $37^{\circ}\text{C}$  show greater decrease in assay with corresponding increases in related impurities.

The proposed shelf life of 24 months at  $2-8^{\circ}\text{C}$  is considered to be acceptable, as 18 months data from three pilot scale batches are available.

An in-use stability study has been performed on two pilot scale batches at  $30^{\circ}\text{C}$ . Based on the results of the study, an in-use period of 42 days at temperatures not above  $30^{\circ}\text{C}$  is acceptable.

Photo stability testing has been conducted on all applied products. Results show that the product is light sensitive. However, the product is adequately protected in the marketing pack or when assembled in InnoLet<sup>®</sup> or FlexPen<sup>®</sup>.

Three production scale batches have been produced and a commitment is given that these batches will be included in stability studies

### **Discussion on chemical, pharmaceutical and biological aspects**

In general, the different aspects of the chemical, pharmaceutical and biological documentation are satisfactorily addressed. The development of the product went through some process changes. During early development insulin detemir was produced from a dedicated insulin detemir precursor; as drug development progressed a new and more specific acylation method was developed. Consequently, a production strategy was adopted, in which the insulin human precursor could be used as the starting material. The comparison of active substance from both processes has confirmed that the structural and physico-chemical properties of active substance from the two processes are similar.

The concerns identified during the procedure have been addressed by clarification and/or commitments. The proposed use of alternative carbon sources (glucose / sucrose) for fermentation for production of the bulk substance has been further documented during the procedure with pilot scale data that indicate that the product quality is not influenced. The applicant also implemented quality criteria with adequate alert limits to monitor column performance (purification capacity, separation, carry-over of proteins and viruses) during re-use. Another concern was to implement a justified limit for summation of storage times of intermediates and bulk substance; based on stability studies, this has been set to 8.5 years. Initially, both the release and end-of-shelf-life specifications for drug product were also considered to be too wide without justification. Specification limits have been tightened or will be re-evaluated based on future batch analysis results, as appropriate.

### **3 Non-clinical aspects**

The non-clinical safety program was designed to compare the pharmacodynamic and toxicological properties of insulin detemir to soluble human insulin or, where appropriate, to Neutral Protamine Hagedorn (NPH) human insulin. In addition to other applicable guidelines, the ICH guideline on "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" and the CPMP "Points to Consider Document on the Non-Clinical Assessment of the Carcinogenic Potential of Insulin Analogues" were taken into account.

All pivotal non-clinical safety studies were GLP-compliant.

#### **Pharmacodynamics**

- *In vitro* and *in vivo* primary pharmacodynamic studies

Primary pharmacodynamics included in-vitro tests for insulin and IGF-I (insulin-like growth factor I) receptor binding, tyrosine kinase stimulation, fat cell lipogenesis and hypoglycaemic activity in non-diabetic and diabetic animal models. Contrary to other insulin analogues, insulin detemir was consistently less potent than human insulin in all in-vitro assays. Depending on the assay, the potency was 2- to 10-fold lower. In vivo, it was equipotent in dogs and pigs, 6-fold less potent in rats and > 15 times less potent in mice and rabbits, the species traditionally used to determine the biological potencies of insulins. In clinical studies, the molar potency of insulin detemir was approximately 1/4 of that of human insulin, which is within the range observed in vitro. As 1 unit of human insulin equals 6 nmol, the applicant has defined 1 unit of insulin detemir as 24 nmol or 0.142 mg of the salt-free, anhydrous protein (MW = 5916.9). The lower potency of insulin detemir relative to human insulin is attributed to the myristic acid moiety being sufficiently close to the receptor recognition site to interfere with insulin receptor binding. As the binding site on the insulin receptor is not identical across species, the degree of interference may vary according to species. Thus, in-vitro binding studies using human, rat, pig and dog insulin receptors showed that insulin detemir had a relatively lower affinity to human and rat than to pig and dog insulin receptors. Another factor contributing to the observed species differences in potency in vivo is inter-species variations in the binding of insulin detemir to albumin and, consequently, in the volume of distribution and clearance relative to human insulin.

- Pharmacodynamic drug interactions

The pharmacodynamic interactions of insulins are well known and therefore were not investigated.

- General and safety pharmacology programme

Whereas other insulin analogues do not have secondary pharmacodynamic effects, insulin detemir is chemically modified through the covalent binding of myristic acid to the  $\epsilon$ -amino group of the C-terminal lysine in the B-chain (B29). To investigate whether this chemical modification could lead to unexpected effects, a battery of screening tests comprising 64 different receptors and subtypes has been performed. Insulin detemir had no functional activity in any of these tests.

In safety pharmacology tests, insulin detemir caused slight CNS depression, slight increases or decreases in blood pressure and a transitory decrease in urine specific gravity that likely were the result of treatment-induced hypoglycaemia.

A hERG (human ether-a-go-go-related gene) ionic current assay and several in-vivo ECG assessments in anaesthetised and conscious animals found no signal for potential risk of QT prolongation or other cardiac effects in humans.

### **Pharmacokinetics**

Insulin detemir was generally well absorbed after s.c. injection, with an overall bioavailability of 38-60% in all species investigated. The elimination half-life was consistently longer after s.c. than i.v. administration, confirming the sustained-release nature of the solution when injected s.c. A low distribution volume ranging from 0.05-0.25 l/kg indicated that distribution is limited to the extracellular space. In rodents and in subchronic dog studies, females tended to show higher  $C_{max}$  and AUC values and exhibited more pronounced accumulation. Similar gender differences were not encountered in humans. Antibody formation in chronically exposed animals was too low to have an impact on kinetics. Contrary to human insulin, insulin detemir is highly bound to serum albumin.

Conventional tissue distribution studies were conducted in rats after s.c. administration of insulin detemir labelled with  $^{125}I$  at amino acid A14 or with  $1-^{14}C$  myristic acid, but were of difficult interpretation due to the rapid metabolism of the test materials. Free iodide accounted for most of the radioactivity in the  $^{125}I$ -insulin detemir studies. The results of the studies performed with  $^{14}C$ -insulin detemir seem to be insufficient, as the pattern of distribution is only in line with the expected distribution of degradation products, such as fatty acids, of insulin detemir. Another study in rats with  $I^{125}$ -labelled insulin detemir or human insulin i.v. was performed with measurements made at 5 minutes, i.e. when interference from radioactive metabolites and degradation products would be minimal. There was no difference in the distribution to lipid-rich tissues, whereas insulin detemir produced higher counts in plasma and highly perfused organs and lower counts in the renal cortex, as expected from the high albumin binding and low clearance of the product.

Limited metabolism studies indicated that insulin detemir is first cleaved at the disulphide bridges whereupon the A- and B-chains are hydrolysed to smaller peptide fragments. These include fragments incorporating the lysine residue at B29 and all or part of the myristic acid moiety attached to its  $\epsilon$ -amino group. In liver cells in vitro, metabolic patterns were qualitatively similar in humans and the mouse, rat, rabbit and dog. Metabolism was less extensive in renal compared to liver cell extracts and produced similar metabolites in human and rat materials. Insulin detemir did not induce cytochrome CYP450 in the rat. The potential for inhibition was not investigated. However, proteins are not known to inhibit the cytochrome system. Moreover, the maximum human plasma level of 10 nM is unlikely to cause any clinically relevant interactions.

In rats and dogs administered insulin detemir labelled with  $1\text{-}^{14}\text{C}$  myristic acid, radioactivity was mainly excreted as  $\text{CO}_2$  in exhaled air, with lesser amounts excreted in the urine and the faeces. Excretion was slow and a substantial fraction was incorporated into carcass constituents. These findings indicate that the fatty acid component undergoes degradation into smaller fragments that enter the physiological pool of short-chain fatty acids. Chain A and deacylated chain B peptides are expected to be metabolised like those of human insulin.

Intact insulin detemir was excreted in the milk of lactating rats at concentrations up to 15 nM or 10 times higher than in plasma. This finding can probably be extrapolated to humans, as human insulin is excreted in the milk of diabetic women at a similar multiple.

In all species investigated, 97-99% of insulin detemir was bound to plasma, lymph and subcutaneous albumin. This binding occurs through the fatty acid moiety and probably contributes to the protracted hypoglycaemic activity of the drug product. As there are 3 high-affinity fatty acid binding sites on the albumin molecule and the concentration of albumin in blood is 0.6 mM, clinically relevant plasma concentrations of free fatty acids and albumin-bound drugs are unlikely to result in any perceptible displacement of insulin detemir. This notion was supported by several experiments. Thus, when the level of free fatty acids was increased to the upper bound of clinically relevant levels, there was no displacement of insulin detemir in human plasma in vitro or changes in its kinetics in pigs in vivo. Likewise, there was no displacement of insulin detemir in *in-vitro* interaction studies with a range of albumin-bound drugs such as warfarin, phenylbutazone, diazepam, valproate, furosemide, tolbutamide, glibenclamide, repaglinide, nicardipine, ibuprofen and acetylsalicylic acid.

## **Toxicology**

### *Single dose toxicity:*

In i.v. and s.c. single-dose studies in rats and mice, high doses of insulin detemir caused death due to hypoglycaemia.

### *Repeat dose toxicity:*

S.c. repeat-dose toxicity studies were conducted in rats and dogs. for up to 6 and 12 months, respectively.

<b>Species / no./sex/group</b>	<b>Duration</b>	<b>Dose (nmol/kg/day)</b>
Sprague-Dawley rats/12	4 weeks	0, 30, 96, 300
Sprague-Dawley rats/25	13 weeks	0, 30, 96, 300
Sprague-Dawley rats/25	26 weeks	0, 30, 96, 300
Dogs/4	4 weeks	0, 3, 6, 9
Dogs/4	13 weeks	0, 1.8, 3.6, 7.2
Dogs/4	26 weeks	0, 1.8, 3.6, 7.2
Dogs/4	52 weeks	0, 1.8, 3.6, 7.2

Signs of systemic toxicity were limited to effects on plasma glucose, small decreases in serum protein and albumin, urea and magnesium and minor changes in a few organ weights, notably the liver in the rat and adrenals in the dog. These findings, which were fully reversible, were also made in the NPH human insulin satellite groups and are therefore considered to be due to exaggerated pharmacodynamic

effects. The only tumours in the 6-month rat study were a mammary fibroadenoma in the mid-dose insulin detemir group and a mammary adenocarcinoma in the NPH human insulin group.

Antibody formation was minimal and did not compromise the interpretation of the data.

#### *Genotoxicity:*

Although not applicable to biotechnology-derived pharmaceuticals, insulin detemir was tested for gene mutations in bacteria and for chromosome aberrations in vitro and in vivo. As expected, there was no evidence of genotoxic potential in any of these tests.

#### *Carcinogenicity:*

Standard carcinogenicity studies were not performed.

Insulin detemir was tested for in vitro mitogenic potency. Relative to human insulin, the albumin-corrected mitogenic potency was 9% in CHO-K1 cells, 15% in human mammary cancer fibroblasts (MCF-7 cells), 11% in a human osteosarcoma cell line and 25% in L6-hIR cells. Based on these data, the mitogenic potency of insulin detemir in vitro seems to be reduced relative to human insulin to approximately the same extent as its binding affinity for the insulin and IGF-1 receptors.

The effect of insulin detemir on in-vivo cell proliferation in Sprague-Dawley rats was studied retrospectively in toxicity studies of 3 and 6 months duration. The 3-month study indicated that insulin detemir produced higher labelling indices in mammary gland than the vehicle control, whereas no difference between vehicle control and insulin detemir was seen in the 6-month study. Nevertheless, retrospective data did not compare the mitogenic potential of insulin detemir to that of human insulin. Therefore a prospective 4-weeks/6-month study, including human insulin as comparator, was initiated. Interim results confirmed the finding in the 3-month retrospective study that insulin detemir had a modest proliferative effect in the mammary gland of young female rats. In addition, insulin detemir and human insulin were found to stimulate rat mammary gland cell proliferation to the same extent. See discussion on toxico-pharmacological aspects

#### *Reproduction Toxicity:*

The tests for reproductive and developmental toxicity comprised Segment I, II and III studies in rats and a Segment II study in rabbits. These studies meet the requirements of the CPMP "Points to Consider on the Need for Assessment of Reproductive Toxicity of Human Insulin Analogues". NPH human insulin was used as reference product and toxicokinetics were included in all studies. The reproductive and developmental toxicity of insulin detemir was similar to that of NPH human insulin.

#### *Local Tolerance:*

In local tolerance studies in pigs, the drug product was slightly better tolerated than equivalent volumes of NPH human insulin.

#### *Immunotoxicity studies:*

Antibody formation to insulin detemir was determined in most pharmacokinetic and toxicity studies. In addition, a formal study was conducted in rabbits to compare the immunogenicity of insulin detemir, NPH bovine and NPH porcine insulin. Overall, antibody formation was biologically insignificant. This finding, however, is not predictive of the potential for antibody formation in humans.

### ***Environmental Risk Assessment:***

The expected risk to the environment is negligible.

### **Discussion on toxico-pharmacological aspects**

Insulin detemir binds to insulin receptors with approximately 25% affinity compared to human insulin. Insulin detemir activates the insulin receptor to the same extent as human insulin.

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity to reproduction.

In vitro, the metabolic to mitogenic potency ratio was similar for insulin detemir and human insulin. Retrospective and 4-weeks prospective in-vivo proliferation studies in the rat showed that insulin detemir had a modest proliferative effect in the mammary gland of young female animals. The magnitude of this effect was similar for insulin detemir and human insulin. The overall conclusion from these investigations is that the mitogenic potential of insulin detemir does not raise concern. Results at 6-month of the ongoing prospective study could be reported post-approval.

Overall, the data from the toxicology programme did not raise concerns for the safe use of insulin detemir

## **4 Clinical aspects**

The clinical development program, designed to provide documentation of the safety and efficacy of the insulin detemir in the treatment of type 1 and type 2 diabetes mellitus, consisted of pharmacology trials in healthy subjects or patients with type 1 or 2 diabetes, short-term trials in patients with type 1 or 2 diabetes, 10 intermediate and long-term trials in patients with type 1 or 2 diabetes, and, ongoing trials in patients with type 1 or 2 diabetes.

Although the majority of the development program was performed before the CPMP “Note for guidance on clinical investigations of medicinal products in the treatment of diabetes mellitus” (EMA/CPMP/EWP/1080/00) was adopted, the development program is broadly speaking in accordance with this guideline.

Four short-term therapeutic trials in subjects with type 1 and type 2 diabetes (006, 1038, 1255, and 2006) were performed. These are considered exploratory therapeutic trials.

The 10 intermediate and long-term trials are considered confirmatory therapeutic trials that provide the main evidence for the efficacy and safety of insulin detemir in the treatment of patients with diabetes mellitus and support the recommended treatment regimens.

According to the applicant, data from all clinical studies, regardless of country, were conducted to the same standards and according to GCP and the Declaration of Helsinki.

### **Clinical pharmacology**

The application was supported by 29 clinical pharmacology studies. Furthermore, three in vitro studies, dealing with plasma protein binding were submitted.

#### ***Pharmacokinetics***

The pharmacokinetic properties of insulin detemir have been studied in healthy subjects, subjects with type 1 diabetes, subjects with type 2 diabetes, children, elderly, subjects with renal impairment and subject with hepatic impairment, have been studied after s.c. administration.

A specific enzyme linked immunosorbent (ELISA) assay was used to determine detemir concentrations in plasma, serum, and interstitial fluid samples. The assay gives a measure of the total (free and albumin bound) insulin detemir concentration.

The pharmacokinetic profile of insulin detemir has been thoroughly evaluated. Following s.c. and i.v. administration of detemir, the pharmacokinetic profile is consistent and predictable across the target population. The data is generally consistent with those obtained in healthy subject while minor and clinically insignificant differences are found compared to subjects with type 2 diabetes.

- Absorption and Bioavailability

With the exception of prolongation of time to maximum concentration at increasing doses, no evidence of dose-dependent pharmacokinetics within the relevant therapeutic dose-range is apparent. The applicant has provided a statistical analysis that confirms a linear dose-AUC relationship and a linear dose-concentration relationship for insulin detemir. Maximum plasma concentrations of insulin detemir are reached about 6 to 8 hours after s.c. administration with a slight tendency to increased values at higher doses. Absolute bioavailability upon s.c. administration is 64, 59 and 65% following s.c. injection in the abdomen, thigh and deltoid, respectively. Insulin detemir AUC<sub>inf</sub>, AUC<sub>0-5h</sub> and C<sub>max</sub> are significantly higher (approximately 10%, 35%, and 20% respectively) following s.c. injection in the abdomen or deltoid, as compared to s.c. injection in the thigh. The observed differences indicate that, as with other insulin preparations, subjects treated with insulin detemir should be advised to rotate injection sites within the same body region.

As with other insulin preparations, the insulin detemir AUC<sub>inf</sub>, AUC<sub>0-5h</sub> and C<sub>max</sub> are significantly increased following i.m. administration (by approximately 15%, 150%, and 72%), as compared to s.c. administration in the thigh. Therefore, patients should follow the generally recommended injection techniques for avoiding i.m. administration.

Within-subject pharmacokinetic variability was significantly less compared to NPH insulin and insulin glargine.

- Distribution

As opposed to human insulin, insulin detemir is highly protein-bound which is reflected in the distributional parameters of the product. The apparent volume of distribution is about 0.1 l/kg, which reflects the high degree, 98-99%, binding of the drug to albumin. Unsurprisingly, the concentration gradient between serum and interstitial fluid was significantly higher for insulin detemir than for human insulin.

- Metabolism and elimination

Insulin detemir is eliminated through extraction and metabolism. Insulin detemir metabolism is initiated with a cleavage of the disulphide bridges between the A- and the B-chain of insulin, resulting in inactive metabolites of detemir that are further degraded. Total splanchnic extraction was about 58% compared to 78% for human insulin. Total extraction by adipose tissue was 6 and 8% for detemir and human insulin, respectively. No net extraction by muscle tissue could be detected. As expected from the distributional features of insulin detemir, the clearance was found in i.v. studies to be lower (1.8 to 2.7 ml/min/kg across trials) than for human insulin (15.8 to 19.6 ml/min/kg across trials) and the initial half-life was longer, 19 to 25 min for insulin detemir (across trials) versus 2.4 min for human insulin. The half-life after s.c. administration was considerably longer, being about 3 to 6 h in healthy subjects and about 5 to 7 hours in subjects with type 1 diabetes.

- Special populations

Possible differences in concentration-time curves for insulin detemir were investigated in *children* and compared with adolescents and adults with type 1 diabetes. In total, 13 prepubertal children (6 to 12 years of age), 10 adolescents (13 to 17 years of age) and 11 adults (18 to 65 years of age) with type 1 diabetes received a single s.c. doses of 12 nmol/kg of insulin detemir. There does not appear to be consistent differences of C<sub>max</sub>, T<sub>max</sub> or T<sub>1/2</sub> between different age groups for insulin detemir.

There was no clinically relevant difference in pharmacokinetics of insulin detemir between elderly and young subjects or between subjects with renal or hepatic impairment and healthy subjects. No clinically relevant differences in the pharmacokinetics of insulin detemir are expected between healthy subjects and subjects with renal or hepatic impairment, based on the studies performed. As the

pharmacokinetics of insulin detemir has not been studied extensively in these populations, it is advised to monitor plasma glucose closely in these populations

With respect to gender differences and with respect to differences between Caucasian and Japanese subjects, no clinically significant differences of insulin detemir pharmacokinetics were found in these populations.

- Interaction studies:

No clinical studies on drug-drug interactions with insulin detemir have been performed. In vitro studies of cytochrome P450 inhibition were not performed as proteins are generally not inhibitors of this system, and insulin detemir did not induce the P450 system in dogs. In vitro studies did not suggest a potential for interactions related to protein binding.

A study showed that while it is possible to self-mix insulin detemir and insulin aspart before injection, the concentration-time curves of the individual insulin preparations are altered by mixing as compared with separate injection. A warning on this issue has been included in section 4.4 of the SPC.

- Bioequivalence studies:

Three formulations were used during clinical development. Bioequivalence in terms of AUC was demonstrated while  $C_{max}$  was statistically significantly about 20 % lower for the 2400 nmol/ml formulation compared to the other formulations used. The latter is not of clinical significance as dose-adjustments are made on an individual basis.

### Pharmacodynamics

The single dose and steady state pharmacodynamic properties of insulin detemir have been evaluated in subjects with diabetes and in healthy subjects following i.v. and s.c. administration. The focus of the pharmacodynamic endpoint was the glucose-lowering effect. The glucose-lowering effect was evaluated during euglycaemic clamps lasting up to 24 hours after insulin administration.

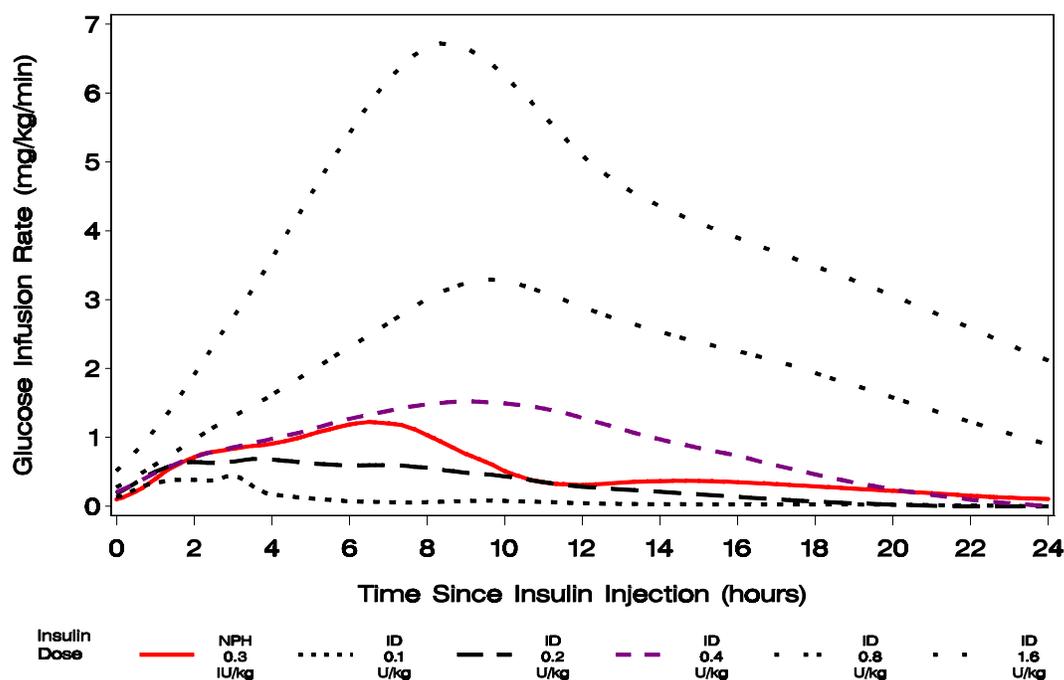
Pharmacodynamic results seem consistent in the target population and across other populations studied.

Insulin detemir exerts its biological effect via binding to the insulin receptor. Insulin detemir binding to the insulin and IGF-I receptors is about 20 – 30% compared to that of human insulin. This corresponds well to the relative potency of insulin detemir found in these studies and in the confirmatory studies.

Insulin detemir pharmacodynamics, primarily assessed by euglycaemic clamp studies, show linear dose-response and concentration-response within the relevant therapeutic dose-range. The applicant has provided a relevant statistical analysis that confirms a linear exposure (AUC detemir) – response (AUC GIR [glucose infusion rate]) relationship. The analysis could not confirm a linear  $C_{max}$ -GIR $_{max}$  relationship.

The time-effect profile of insulin detemir at steady state was comparable to the profile of human insulin. There was no significant difference in the glucose-lowering effect during each 12-hour interval or over 24 hours as AUC GIR was comparable for insulin detemir and NPH insulin. No differences in fluctuation were found. The duration of action at equipotent doses of detemir and NPH insulin was estimated to be about 4 hours longer for insulin detemir. This result is based on an interpolation of results from two different insulin detemir doses, as a direct comparison at equipotent doses was not performed.

The following figure illustrates mean glucose infusion rate (GIR) curves following five s.c. doses of insulin detemir ranging from 0.1 to 1.6 U/kg and one s.c. dose of NPH insulin (0.3 IU/kg), based on data of trial 1338 comparing the glucose-lowering effects of insulin detemir and NPH insulin during a 24-hour euglycaemic clamp in a cross-over design with 12 subjects with type 1 diabetes. The molar ratio between insulin detemir and NPH insulin was estimated to be 3.9 to 1 based on equal AUC of the glucose infusion rate.



Within-subject pharmacodynamic variability is significantly less than for NPH insulin and insulin glargine.

The following table shows within-subject Variance in Pharmacodynamic Endpoints for Insulin Detemir, NPH Insulin or Insulin Glargine in Subjects with Type 1 Diabetes in Trial 1450 (single s.c. dose euglycaemic clamp trial).

Insulin	N <sup>a</sup>	Within-subject Variance			
		AUC <sub>GIR,0-12h</sub> <sup>b</sup>	AUC <sub>GIR,0-24h</sub> <sup>b</sup>	GIR <sub>max</sub> <sup>b</sup>	t25%AUC <sub>GIR</sub>
Insulin detemir	18	0.072	0.074	0.053	0.903
NPH insulin	18	0.352	0.466	0.209	2.417
Insulin glargine	16	0.210	0.231	0.130	3.261

Dose was 0.4 (I)U/kg.

<sup>a</sup> N is number of subjects with 4 glucose clamps.

<sup>b</sup> Variance was derived from log transformed endpoints.

The metabolic effects as assessed by studies of glucose and lipid metabolism are comparable for detemir and human insulin.

### Clinical efficacy

Insulin detemir is indicated for use in patients with diabetes mellitus. In addition to pharmacology trials, the clinical development included 4 exploratory trials, 8 confirmatory trials plus 2 extension trials and 2 ongoing trials, performed in patients with type 1 or type 2 diabetes.

### Dose-response studies and main clinical studies

#### Dose response studies

Four exploratory therapeutic short-term trials were performed (006, 1038, 1255 and 2006) with early formulations that will not be marketed (600 nmol/mL or 1200 nmol/ml). All of these trials were performed to investigate the potency of insulin detemir compared to NPH insulin in small numbers of subjects with type 1 or type 2 diabetes. The efficacy results of these trials do not substantially contribute to the description of the product due to the short duration of treatment. The trials indicated

that an increase in molar dose of insulin detemir was required compared to NPH insulin to obtain comparable glucose levels.

Clinical pharmacology trial 1338 was later investigating 12 patients receiving insulin detemir 2400 nmol/mL 0.1, 0.2, 0.4, 0.8 and 1.6 U/kg s.c. vs. NPH insulin 0.3 U/kg. The molar ratio between insulin detemir and NPH insulin was estimated to be 3.9 to 1 based on equal AUC of the glucose infusion rate during an isoglycemic clamp.

Based on the early confirmatory trials and trial 1338 these results confirming a molar dose ratio of approximately 4:1 as regards the glucose-lowering effect and based on the intention to provide a solution that on a millilitre to millilitre basis had a similar glucose lowering effect as standard NPH insulin solutions (100 IU/ml), a preparation of 2400 nmol/mL of insulin detemir was chosen for the late phase III trials.

#### Therapeutic confirmatory trials

A total of 10 clinical trials were performed to support the efficacy and safety of insulin detemir. Eight studies having a treatment period of 4-6 months, and 2 extension studies with a total treatment period of 12 months.

The table below gives an overview of the clinical trials, distinguishing trials performed in patients with type 1 and type 2 diabetes, as well as using the early 1200 nmol/ml formulation or the 2400 nmol/ml to-be-marketed formulation.

<b>Trial ID</b>	<b>No. Subjects Exposed (IDet/NPH)</b>	<b>Treatment</b>	<b>Treatment Duration</b>	<b>Primary Endpoint</b>	<b>Secondary Efficacy Variables and Other Variables Evaluated</b>
<b>Type 1 Diabetes – Early Confirmatory Therapeutic Trials using the Early 1200 nmol/mL Preparation</b>					
1181	236/224 randomised 1:1	Basal: IDet or NPH 2 x daily  Bolus: HIS	6 months	HbA <sub>1c</sub> after 6 months	9-point blood glucose profiles Fasting plasma glucose Within-subject variation in FBG Hypoglycaemia Weight Quality of Life
1243 extension of 1181	154/134 entered extension	Basal: IDet or NPH 2 x daily  Bolus: HIS	6 months	Adverse event incidence	HbA <sub>1c</sub> after 12 months 9-point blood glucose profiles Fasting plasma glucose Hypoglycaemia Antibodies Weight Quality of Life
1205	301/146 randomised 2:1	Basal: IDet or NPH 2 x daily  Bolus: Iasp	6 months	HbA <sub>1c</sub> after 6 months	9-point blood glucose profiles Fasting plasma glucose Within-subject variation in FBG 8-h nightly plasma glucose Hypoglycaemia Weight
1316 extension of 1205	216/99 entered extension	Basal: IDet or NPH 2 x daily  Bolus: Iasp	6 months	Adverse event incidence	HbA <sub>1c</sub> after 12 months 9-point blood glucose profiles Fasting plasma glucose Hypoglycaemia Weight
<b>Type 1 Diabetes – Late-Development Trials using the To-Be-Marketed 2400 nmol/mL Preparation</b>					
1335	491/256 randomised 2:1	Basal: IDet or NPH 1 x daily  Bolus: HIS	6 months	HbA <sub>1c</sub> after 6 months	9-point blood glucose profiles Fasting plasma glucose Within-subject variation in FBG 24-h continuous glucose profiles Hypoglycaemia Antibodies Weight
1447	271/129 randomised 1:1:1 (IDet:IDet: NPH)	Basal: IDet(morn+dinner) IDet (morn+bed) NPH(morn+bed)  Bolus: Iasp	4 months	HbA <sub>1c</sub> after 4 months	10-point blood glucose profiles Fasting plasma glucose Within-subject variation in FBG 24-h continuous glucose profiles Hypoglycaemia Weight
1448	276/132 randomised 1:1:1 (IDet:IDet:NPH)	Basal: IDet every 12 h IDet (morn+bed) NPH (morn+bed)  Bolus: Iasp	4 months	HbA <sub>1c</sub> after 4 months	10-point blood glucose profiles Fasting plasma glucose Within-subject variation in FBG 24-h continuous glucose profiles Hypoglycaemia Weight

<b>Type 2 Diabetes – Early Confirmatory Therapeutic Trials using the Early 1200 nmol/mL Preparation</b>					
1166	221/218 randomised 1:1	Basal: IDet or NPH 2 x daily  Bolus: None	6 months	HbA <sub>1c</sub> after 6 months	9-point blood glucose profiles Fasting plasma glucose Within-subject variation in FBG Hypoglycaemia Weight
<b>Type 2 Diabetes – Late-Development Trials using the To-Be-Marketed 2400 nmol/mL Preparation</b>					
1336	341/164 randomised 2:1	Basal: IDet or NPH 1 or 2 x daily  Bolus: Iasp	6 months	HbA <sub>1c</sub> after 6 months	9-point blood glucose profiles Fasting plasma glucose Within-subject variation in FBG 24-h continuous glucose profiles Hypoglycaemia Weight Quality of Life
1337	309/158 randomised 2:1	Basal: IDet or NPH 1 x daily  Bolus: None OADs: Metformin	6 months	HbA <sub>1c</sub> after 6 months	9-point glucose profiles Fasting plasma glucose Within-subject variation in FBG Hypoglycaemia Weight

IDet = insulin detemir; NPH = NPH insulin; HSI = human soluble insulin; IAsp = insulin aspart

All trials were multicentre, randomised, parallel-group and open-label comparing insulin detemir with human NPH insulin, the standard insulin providing basal insulin supply. All trials were open-labelled, as the two products are easily distinguishable from each other on visual inspection – insulin detemir being a clear, transparent solution, and the comparator (NPH insulin) an opaque suspension. A double-dummy technique was considered impractical and potentially hazardous, due to the risk of medication errors. In addition, the insoluble NPH insulin was not available in a placebo formulation.

The basal insulin regimen was once or twice daily at bedtime or at morning and at bedtime, except for 2 studies where insulin detemir was given at morning and at dinner or with a 12-hour interval. All trials in type 1 diabetes (1181, 1205, 1335, 1447, 1448) and one trial in type 2 diabetes (1336) employed a basal-bolus regimen, using either human soluble insulin or the rapid-acting insulin analogue, insulin aspart. The remaining two trials in type 2 diabetes used basal insulin as monotherapy (1166) and in combination with metformin (1337), respectively.

All trials included subjects who were previously treated with insulin, except for Trial 1337, in which all subjects were insulin naïve at baseline. The glycaemic targets used as goals for titration of the daily insulin dose were the same in all trials: fasting/preprandial blood glucose between 4.0-7.0 mmol/l (72-126 mg/dl), postprandial blood glucose less than 10.0 mmol/l (180 mg/dl) and nightly blood glucose between 4.0-7.0 mmol/l (72-126 mg/dl).

In the long-term extension Trials 1243 and 1316, subjects continued on the treatment to which they were randomised originally, and thus the trials cannot be considered randomised during the extension period, due to selection bias.

The main inclusion and exclusion criteria that were common to the trials are mentioned below.

Inclusion criteria: duration of diabetes ≥ 12 months, age ≥ 18 years of age (for type 1 diabetes) or ≥ 35 years of age (for type 2 diabetes), body mass index (BMI) ≤ 35.0 kg/m<sup>2</sup>, HbA<sub>1c</sub> ≤ 12.0% based on analysis from central laboratory and basal insulin requirement ≥ 30% of the total daily insulin dose  
Exclusion criteria: proliferative retinopathy, recurrent major hypoglycaemia, known unawareness of hypoglycaemia, pregnancy and severe concomitant diseases.

The primary objective of the confirmatory therapeutic trials was to compare the effect of insulin detemir with that of NPH insulin on glycaemic control as measured by non-inferiority of HbA<sub>1c</sub> in subjects with diabetes.

The primary efficacy endpoint for all of the confirmatory therapeutic trials was the fraction of glycated haemoglobin, HbA<sub>1c</sub>.

Secondary endpoints for the assessment of efficacy include: fasting plasma glucose, 9- or 10-point blood glucose profiles (home measurements), 24-hour glucose measured using the MiniMed Continuous Glucose Monitoring System, 8-hour nightly plasma glucose profiles, and within-subject variability in fasting blood glucose. Furthermore, hypoglycaemia, body weight, and insulin antibodies have implications for the evaluation of efficacy, and are therefore also addressed in relation to clinical effectiveness.

The statistical analyses of efficacy and safety in all confirmatory therapeutic trials are based on the intention-to-treat (ITT) analysis set, defined as all randomised subjects exposed to at least one dose of trial product. In general, the primary objective of the trials is to demonstrate that the glycaemic control, measured by HbA<sub>1c</sub>, achieved after treatment with insulin detemir, is at least as good as the glycaemic control achieved after treatment with NPH insulin (non-inferiority). Non-inferiority is claimed if the upper limit of the 95% confidence interval for the difference is less than 0.4%. Superiority is claimed if the upper limit of the 95% confidence interval for the difference is lower than 0%.

In Trials 1447 and 1448, in which three different treatment regimens were used, the primary objective was to compare the outcomes in the three treatment groups. Where no significant difference was found in the three-way comparison, results for the two insulin detemir treatment groups in each trial have been pooled.

### Results

A total of 2446 patients with diabetes mellitus were randomised and exposed to treatment with insulin detemir (1575 patients with type 1 diabetes and 871 patients with type 2 diabetes). As the comparator treatment, 1427 patients were randomised and exposed to NPH insulin (887 patients with type 1 diabetes and 540 patients with type 2 diabetes).

Overall the completion rate was high in the confirmatory therapeutic trials: 94% for both insulin detemir and NPH insulin in type 1 diabetes, and 87% and 92% for insulin detemir and NPH insulin, respectively, in type 2 diabetes. In subjects with type 2 diabetes, those on insulin detemir withdrew more frequently due to ineffective therapy (4.6%) than those on NPH insulin (0.7%). The majority (60%) of withdrawals due to ineffective therapy in the insulin detemir group arose in Trial 1166, in which many subjects failed to achieve the appropriate dose during the trial. The early formulation of insulin detemir required injection volumes that were unacceptably large in order to achieve the relatively high doses needed for basal insulin treatment in poorly controlled subjects with type 2 diabetes.

Overall, the study populations in the confirmatory therapeutic trials were comparable within each study, without major differences between treatment groups. Subjects with type 1 diabetes had a mean age of approximately 40 years in all trials, ranging from 17 to 83 years. Subjects with type 2 diabetes were older, with a mean age of 58 years (range 34-91). Subjects with type 1 diabetes had a mean body weight ranging from 71 to 77 kg in the different trials. Body weight in subjects with type 2 diabetes was generally higher (means from 78 to 90 kg) with greater variation, as expected for the subject population. In general, more males than females were enrolled, with an overall distribution of 57% males and 43% females in all trials combined. The overall mean duration of diabetes was 14 years, with somewhat longer duration in trials in type 1 diabetes (means 15 - 17 years) than in trials in type 2 diabetes (means 9 - 13 years). Mean HbA<sub>1c</sub> levels at baseline were around 8% in most trials, with slightly higher levels in Trial 1448 (type 1 diabetes) and Trials 1166 and 1337 (both type 2 diabetes), in which mean HbA<sub>1c</sub> was closer to 9%.

Prior to the trial, the vast majority of subjects with type 1 diabetes were on a basal-bolus insulin regimen, whereas less than 4% were treated with premixed insulin only. A great diversity was found among pretrial treatments in subjects with type 2 diabetes. Mean daily doses of basal insulin ranged from 0.31 to 0.39 IU/kg (24 to 28 IU) in all but one trial (Trial 1166 in type 2 diabetes), in which considerably higher basal insulin doses were used (mean 0.54 IU/kg; 41 IU absolute). Mean basal and bolus insulin doses (units/kg) are presented for each trial in the table below. All doses of insulin detemir are expressed in the units of the to-be-marketed preparation. Bolus insulin (human soluble insulin or insulin aspart) was used in 8 of the 10 trials.

#### Mean Basal and Bolus Insulin Dose per kg at End of Trial (ITT)

Trial	IDet (U/kg <sup>a</sup> or IU/kg)		NPH(U/kg <sup>a</sup> or IU/kg)	
	Basal	Bolus	Basal	Bolus
<b>Subjects with type 1 diabetes</b>				
1181	0.29	0.43	0.38	0.36
1243 <sup>ext</sup>	0.30	0.43	0.39	0.37
1205	0.42	0.43	0.44	0.36
1316 <sup>ext</sup>	0.43	0.44	0.46	0.37
<b>1335#</b>	0.27	0.47	0.33	0.44
<b>1447#</b>	0.43	0.39	0.38	0.34
<b>1448#</b>	0.49	0.38	0.45	0.38
<b>Subjects with type 2 diabetes</b>				
1166	0.82	-	0.78	-
<b>1336#</b>	0.42	0.46	0.39	0.40
<b>1337#</b>	0.56	-	0.45	-

# Late development trials

a Insulin detemir doses are in units (U): 1 unit = 24 nmol; NPH insulin doses are in units (IU): 1 unit = 6 nmol

Results on HbA<sub>1c</sub> are shown in the tables below.

#### ANOVA of HbA<sub>1c</sub> (%) at End of Trial (ITT)

Trial	IDet		NPH		Difference: IDet – NPH [95% CI]
	N	End	N	End	
<b>Subjects with type 1 diabetes</b>					
1181	210	7.68	206	7.59	0.09 [-0.05, 0.22]
1243 <sup>ext</sup>	139	7.88	124	7.78	0.10 [-0.08, 0.27]
1205	280	7.60	139	7.64	-0.04 [-0.22, 0.13]
1316 <sup>ext</sup>	210	7.53	96	7.59	-0.06 [-0.30, 0.17]
<b>1335#</b>	464	8.46	236	8.58	-0.11 [-0.24, 0.02]
<b>1447#</b>	256	7.66	125	7.73	-0.07 [-0.22, 0.08]
<b>1448#</b>	267	7.76	125	7.94	-0.18 [-0.34, -0.02]
<b>Subjects with type 2 diabetes</b>					
1166	178	9.36	203	8.70	0.66 [0.44, 0.98]
<b>1336#</b>	315	7.63	155	7.48	0.16 [0.00, 0.31]
<b>1337#</b>	261	8.40	134	7.89	0.51 [0.28, 0.74]

# Late development trials

## Mean HbA<sub>1c</sub> (%) at Baseline and End of Trial (ITT)

Trial	Idet				NPH			
	N	Base	End	Change (Bas-End)	N	Base	End	Change (Bas-End)
<i>Subjects with type 1 diabetes</i>								
1181	210	7.63	7.66	0.03	206	7.68	7.61	-0.06
1243 <sup>ext</sup>	139	7.64	7.73	0.09	124	7.67	7.67	0.00
1205	280	8.18	7.62	-0.55	139	8.11	7.61	-0.50
1316 <sup>ext</sup>	210	8.15	7.51	-0.64	96	8.04	7.47	-0.56
1335#	464	8.35	8.30	-0.06	236	8.35	8.41	0.06
1447#	256	8.07	7.61	-0.46	125	8.09	7.70	-0.39
1448#	267	8.64	7.82	-0.82	125	8.51	7.91	-0.60
<i>Subjects with type 2 diabetes</i>								
1166	178	8.93	9.26	0.33	203	8.78	8.53	-0.25
1336#	315	7.87	7.61	-0.26	155	7.76	7.40	-0.36
1337#	261	9.43	8.41	-1.02	134	9.37	7.87	-1.50

### # Late development trials

An exploratory analysis was carried out combining data from only the trials using the to-be-marketed insulin detemir preparation in type 1 diabetes (see table below).

### Combined ANOVA of HbA<sub>1c</sub> (%) at End of Trial in Type 1 Diabetes - Late Development Trials (Trials 1335, 1447, 1448)

Insulin detemir		NPH insulin		Difference (IDet – NPH)	
N	Mean (SE)	N	Mean (SE)	Mean	95% CI
983	8.30 (0.10)	485	8.41 (0.10)	-0.11	[-0.20; -0.01]

Non-inferiority criterion: Upper confidence limit of difference <0.4% (absolute)

Superiority criterion: Non-inferiority met and upper confidence limit of difference <0% (absolute)

Mean: Least square mean, SE: Standard Error of the mean, CI: Confidence interval

In summary, non-inferiority was demonstrated in all trials in type 1 diabetes. Considering the late development pivotal trials in type 1 diabetes, a reduction in HbA<sub>1c</sub> was seen in trial 1447 and 1448 in both Insulin detemir and NPH insulin treated patients. In trial 1335, no such a reduction was observed. In this trial a once daily basal insulin regimen was used. In type 2 diabetes, non-inferiority was demonstrated in only one trial (1336). In trial 1337, in which patients were treated with insulin and metformin, non-inferiority was not proven. In early development trial 1166, non-inferiority was not demonstrated. In this trial there were major inadequacies in dosing; this trial used one of the earlier and less concentrated preparations (1200 nmol/ml), and investigators and subjects were apparently reluctant to titrate the doses intensively enough when faced with the large volumes and apparent high numbers of units for insulin detemir.

### *Fasting plasma glucose*

In general, the results from trials in type 1 diabetes show that insulin detemir in the regimens tested was as effective as or better than NPH insulin in reducing fasting hyperglycaemia.

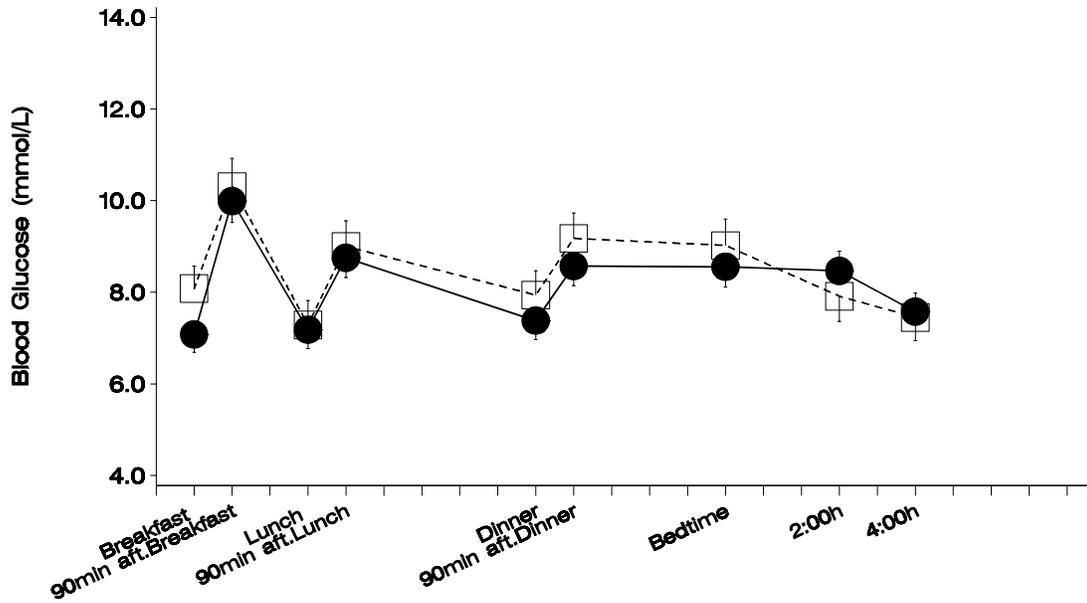
In type 2 diabetes, fasting plasma glucose at the end of trial was comparable between treatments in Trials 1336 and 1337. In Trial 1166, the decline in FPG was smaller in the insulin detemir group than the NPH group, due largely to the inadequate dosing discussed previously.

### *Within subject variation in fasting blood glucose*

Within-subject day-to-day variation was assessed based on self-measured fasting blood glucose toward the end of the 4- and 6-month trials. Fasting blood glucose measurements were taken at home the last 7 days of the treatment period. In both type 1 and type 2 diabetes, within-subject variation, assessed as the standard deviation of the mean (SD), was lower in the insulin detemir treatment group in all trials except Trial 1166, with significant differences in five of the trials

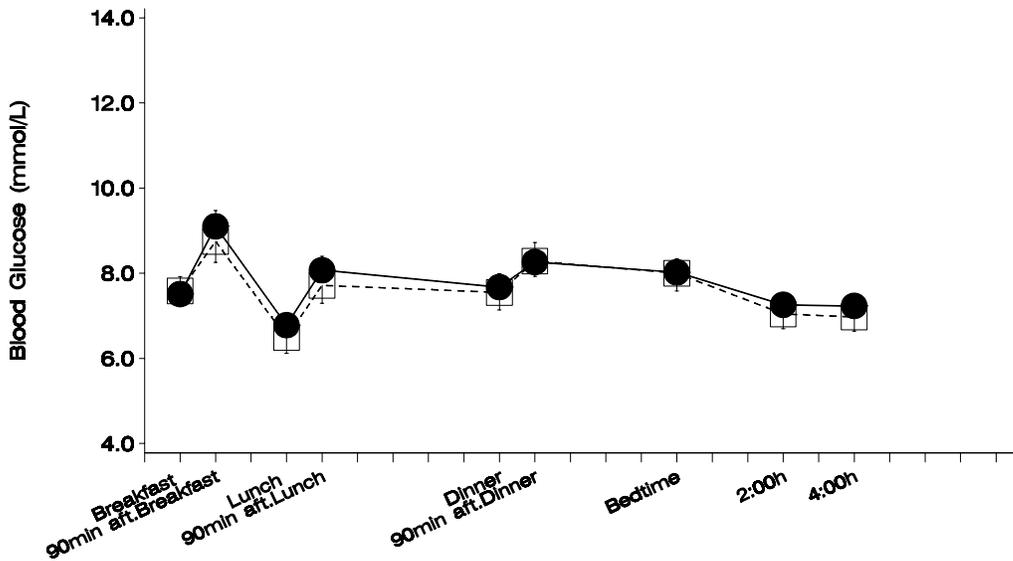
### *9- and 10-point blood glucose profiles*

Glucose profiles from the late-development confirmatory therapeutic trials 1335, (type 1 diabetes) and 1336 (type 2 diabetes), using the to-be-marketed preparation, are presented below.



Time of the Day (Trial Id. 1335)

Treatment Group ●—●—● Insulin detemir □-□-□ NPH insulin



Time of the Day (Trial Id. 1336)

Treatment Group ●—●—● Insulin detemir □-□-□ NPH insulin

### Hypoglycaemia

Hypoglycaemic episodes were classified in the trials as:

a) Major - an episode with severe CNS symptoms consistent with hypoglycaemia in which the patient was unable to treat himself/herself and which had one of the following characteristics:

- Blood glucose < 2.8 mmol/L (50 mg/dL)
- Reversal of symptoms after either food intake or glucagon/iv glucose administration.

b) Minor - an episode with symptoms consistent with hypoglycaemia with:

- Confirmation by blood glucose measurement < 2.8 mmol/L (50 mg/dL) and which was handled by the patient himself/herself, or
  - Any asymptomatic blood glucose measurement < 2.8 mmol/L (50 mg/dL).
- c) Symptoms only - symptoms that are considered to be related to hypoglycaemia but not confirmed by a blood glucose measurement.

The risk of hypoglycaemia is addressed in the context of clinical efficacy, where relative risk of hypoglycaemia has been calculated. Supplementary analyses have been adjusted for differences in glycaemic control (HbA<sub>1c</sub>), in order to ascertain whether the differences found in relative risk could be attributable to individual differences in glycaemic control. Additional analyses investigated nocturnal hypoglycaemic episodes, defined as episodes occurring between 23:00 and 6:00 hours.

Major hypoglycaemic episodes were experienced by approximately 9% of patients with type 1 diabetes and in less than 2% of the patients with type 2 diabetes during the treatment period. The relative risks of having a major hypoglycaemic episode were similar in insulin detemir and NPH insulin in both patient groups.

Minor hypoglycaemic episodes were experienced by approximately 85% of patients with type 1 diabetes and in approximately 21% of the patients with type 2 diabetes.

In summary, data from individual studies are not consistent and the overall rates of hypoglycaemia with Levemir and NPH Insulin are similar. Further analyses of nocturnal hypoglycaemia did not show statistical differences between insulin detemir and NPH Insulin except in type 1 diabetes where there was a lower risk of minor nocturnal hypoglycaemia.

#### *Body weight*

Mean body weight was significantly lower in the insulin detemir group relative to the NPH insulin group at the end of treatment in all trials. The difference in mean body weight changes (insulin detemir - NPH insulin) was between -0.61 kg to -1.58 kg in type 1 diabetes trials and -0.77 kg to -2.00 kg in type 2 diabetes trials. In general, subjects in the insulin detemir group maintained weight or had slight weight reductions, while subjects on NPH insulin tended to increase in weight during the trial. Covariate adjustment for HbA<sub>1c</sub> in the analysis verified that the lower body weight with insulin detemir was independent of individual differences in glycaemic control during treatment.

#### *Nightly 8-Hour plasma glucose profiles*

Nightly 8-hour plasma glucose profiles were assessed in a subset of subjects with type 1 diabetes (IDet, N=88; NPH, N=41) in the early Trial 1205 which was performed with the 1200 nmol/ml preparation. Profiles were based on hourly measurements taken after 6 months of treatment, while subjects were fasting during an overnight stay at the investigational site. The shapes of the nightly plasma glucose profiles were considerably different, reflecting the longer duration of action of insulin detemir compared with NPH insulin. 9 and 10-point self-measured blood glucose profiles showed lower blood glucose values with insulin detemir from 4:00 hours.

#### *Clinical studies in special populations*

No clinical treatment studies were performed in the paediatric population. According to the “Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus” (CPMP, November 2002), these trials are usually required pre-licensing, as tested insulin preparations are to be used in this population. A large (N=338) multicentre therapeutic trial in children and adolescents with type 1 diabetes is currently in progress. The trial is a 26-week, multinational, multi-centre, open-labelled, randomised, parallel efficacy and safety comparison of insulin detemir and NPH insulin in children and adolescents with type 1 diabetes on a basal-bolus regimen. The applicant committed to supply data on clinical efficacy and safety in children and adolescents, after marketing authorisation.

No separate studies were conducted in the elderly population. The clinical development programme included 437 elderly ( $\geq 65$  years of age) subjects (264 treated with insulin detemir and 173 with NPH insulin).

#### Exploratory analysis performed across trials (pooled analyses and meta-analysis).

##### *Continuous Glucose Monitoring System: Excursions and fluctuations*

Analyses were performed to estimate differences in variation between the two treatments using data collected with the Continuous Glucose Monitoring System (CGMS). Glucose excursions were defined as the portion of the individual glucose profiles falling outside of the range from 4 to 10 mmol/L. Low excursions were calculated as the area over the glucose profile and below 4 mmol/L (AOC $<4$  mmol/L). Glucose fluctuations were calculated post-hoc as the total area between the glucose profile and the subject's individual mean glucose level. These analyses express the overall variability in serum glucose levels during the period. Data were obtained in a subset of subjects in the late-development trials 1335, 1447, and 1448 in subjects with type 1 diabetes. Combined analyses across trials in subjects with type 1 diabetes showed reductions in low excursions with insulin detemir, both over the 24-hour period and at night, and the analysis of fluctuations showed lower variability for insulin detemir.

##### *Subpopulations:*

The Applicant analysed efficacy and safety in a large number of subpopulations. No clinically meaningful differences were found. Especially, no effect of age was found with respect to efficacy or the risk for hypoglycaemia. Furthermore, no effect was seen of low albumin levels, defined as albumin  $<35$  g/L. However, the number of patients with low albumin levels was limited (8 type 1 diabetics and 15 type 2 diabetic patients). As a consequence, careful monitoring should be recommended in patients with severe hypoalbuminaemia.

#### Supportive study

Trial 1385 was an open-label, randomised, parallel group comparison of insulin detemir + insulin aspart versus NPH insulin + human soluble insulin on glycaemic control measured by HbA1c in subjects with type 2 diabetes. In total, 449 subjects were screened, 395 subjects were randomised and 378 subjects completed the 22-week trial. The subjects were previously insulin treated and were randomised to either detemir + insulin aspart or NPH + human soluble insulin as basal-bolus regimen with basal insulin injections one or two times daily. The two groups of subjects were comparable with respect to age, BMI, diabetes duration and baseline HbA1c. Treatment with insulin detemir + insulin aspart was found non-inferior to treatment with NPH insulin + human soluble insulin: HbA1c values after 22 weeks of treatment were 7.46 and 7.52% respectively. The trial was a comparison between two different basal insulins and two different bolus insulin preparations, therefore, the effect of insulin detemir per se compared to NPH insulin cannot be evaluated in this trial since the bolus insulin preparations were different in the two study groups. However, the study 1336 has demonstrated that when insulin detemir is used as basal insulin in a basal-bolus regimen (in combination with insulin aspart as bolus insulin) in patients with type 2 diabetes, it provides glycaemic control which is non-inferior to the glycaemic control provided by insulin NPH (in combination with insulin aspart). Thus even considering the limitations of study 1385, it is conceded that insulin detemir (when used as part of basal-bolus regimen) provides acceptable glycaemic control in patients with type 2 diabetes.

#### Discussion on clinical efficacy

For proving efficacy of insulin detemir a total of 10 confirmatory therapeutic trials were performed: eight 4- and 6-months randomised controlled trials and two extension trials (12 months). Five trials and the extension trials were performed in type 1 diabetic patients and three in type 2 diabetic patients.

Two trials (1181, 1205) and their extension (1243, 1316) were conducted with the early 1200 nmol/ml preparation and three trials (1335, 1447, 1448) with the to-be-marketed preparation of 2400 nmol/ml in type 1 diabetic patients. The duration of the later trials was 4-6 months, a minimum duration for

demonstrating efficacy, according to the CPMP Note for Guidance. With respect to the primary endpoint, HbA<sub>1c</sub> after 4-6 months, insulin detemir appeared to be non-inferior to NPH insulin in type 1 diabetic patients. In one trial (1448) the criterion for superiority was met. Considering the pivotal trials in type 1 diabetes, a reduction in HbA<sub>1c</sub> was seen in trial 1447 and 1448 in both insulin detemir and NPH insulin treated patients. In trial 1335, no such a reduction was observed. In this trial a once daily basal insulin regimen was used.

In type 2 diabetic patients, study 1336 demonstrated that when insulin detemir is used as basal insulin in a basal-bolus regimen (in combination with insulin aspart as bolus insulin), it provides glycaemic control, which is non-inferior to the glycaemic control provided by insulin NPH (in combination with insulin aspart). Thus it is concluded that insulin detemir (when used as part of basal-bolus regimen) provides acceptable glycaemic control in patients with type 2 diabetes. However, when used outside the basal-bolus regimen, the efficacy of insulin detemir in type 2 diabetic has not been adequately demonstrated: study 1166 (in which insulin detemir was used as twice daily monotherapy) and study 1337 (in which insulin was used once daily in combination with metformin) failed to demonstrate non-inferiority to insulin NPH (used in similar regimens). Thus it is concluded that insulin detemir should only be used as part of a basal bolus regimen, as reflected in the summary of product characteristics: "Levemir is a soluble long-acting insulin analogue used as basal insulin in combination with meal-related short- or rapid- acting insulin".

Blood glucose levels showed less variation in patients treated with insulin detemir, as compared to NPH treated patients. Fasting blood glucose levels were lower with insulin detemir than with NPH insulin. Results indicate that blood glucose levels with insulin detemir are lower at 4:00 hours and the early morning but this was not accompanied by an increase of hypoglycaemia.

Overall rates of hypoglycaemia with insulin detemir and NPH insulin were similar.

In general, subjects in the insulin detemir group maintained weight or had slight weight reductions, while subjects on NPH insulin tended to increase in weight during the trial. The possible mechanism is unknown even if it could be linked to minor difference in food intake.

Efficacy of insulin detemir was analysed in a large number of subpopulations. Demographic factors studied were sex, age, ethnic origin and BMI. Disease related factors included diabetes duration, lipid disorders, low serum albumin, high serum creatinine, high serum ALAT. Furthermore, the effects of concomitant treatment with drugs influencing glucose metabolism and drugs that bind to albumin were studied. No clinical meaningful differences in any of the subgroups were found for efficacy or safety. However, the number of patients with low serum albumin was small and therefore caution should be recommended in patients with severe hypoalbuminaemia.

It is concluded that for type 1 diabetic patients insulin detemir is as efficacious as NPH insulin after 4-6 months of treatment when given as basal injection 1 to 2 times daily. Long-term efficacy data are limited to the 1200 nmol/ml preparation, and are prone to bias due to the design of the extension studies. For type 2 diabetic patients, insulin detemir was as good as NPH insulin if given with bolus injections with short acting insulin. Combination with metformin or monotherapy did not meet the non-inferiority criterion.

### **Clinical safety**

The safety population consisted of all subjects who were exposed to at least one dose of the trial medication, a total of 3159 subjects exposed to insulin detemir. Safety parameters were derived from clinical pharmacology trials comprising a total of 518 healthy subjects, and patients with type 1 and type 2 diabetes, short-term trials (less than 6 weeks of treatment) comprising a total of 195 patients with type 1 and type 2 diabetes, intermediate and long-term trials (more than 6 weeks of treatment) comprising a total of 2446 patients with type 1 and type 2 diabetes. In total, 388 healthy subjects, 1782 patients with type 1 diabetes and 989 patients with type 2 diabetes comprised the safety database. The majority of subjects were derived from the confirmatory trials (1181, 1205, 1335, 1447, 1448, 1166, 1336, 1337) and 1-year extension trials (1243 and 1316).

### Patient exposure

A total 1248 subject years of exposure to insulin detemir were evaluated, 98% derived from the confirmatory intermediate and long-term trials. In total, 1732 subjects were exposed to insulin detemir for 6 months or more.

### Adverse events and serious adverse event/deaths

The frequency of the most common adverse events (AEs) in subjects with type 1 diabetes in the intermediate and long-term trials are summarised in the table below.

The most common reported adverse events were upper respiratory tract infections, pharyngitis and headaches, diarrhoea and influenza-like symptoms for both the insulin detemir group and the NPH insulin group.

	Insulin Detemir						NPH Insulin					
	HSI		E	IAsp		E	HSI		E	IAsp		E
N	(%)	N		(%)	N		(%)	N		(%)		
Number of Subjects Exposed	727			848			480			407		
All Adverse Events	542(74.6)	2103		609(71.8)	2113		356(74.2)	1428		290(71.3)	976	
RESPIRATORY SYSTEM DISORDERS												
UPPER RESP TRACT INFECTION	213(29.3)	310		184(21.7)	227		126(26.3)	181		89(21.9)	105	
PHARYNGITIS	58(8.0)	75		69(8.1)	88		30(6.3)	37		41(10.1)	47	
CENTR & PERIPH NERVOUS SYSTEM DISORDERS												
HEADACHE	177(24.3)	475		168(19.8)	331		109(22.7)	345		79(19.4)	157	

The vast majority of AE's were classified as mild in severity. The only severe AE's reported in more than 1% of the subjects were hypoglycaemia-related events. The overall AE profile did not differ between insulin detemir and NPH insulin, except for injection site reactions. This AE was reported in 1.3% of the subjects treated with insulin detemir vs. 0.2% of the subjects treated with NPH insulin. Most of these reactions were mild, a few moderate, and no severe reactions were reported.

The frequency of the most common adverse events in subjects with type 2 diabetes in the intermediate and long-term trials are summarised in the table below.

The most common reported adverse events were influenza-like symptoms, upper respiratory tract infections, headaches and diarrhoea and for both the insulin detemir group and the NPH group.

	Insulin Detemir						NPH Insulin					
	Monotherapy		IAsp		Metformin		Monotherapy		IAsp		Metformin	
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Number of Subjects Exposed to	221		341		309		218		164		158	
All Adverse Events	158(71.5)	371	213(62.5)	538	214(69.3)	602	164(75.2)	363	103(62.8)	252	102(64.6)	316
BODY AS A WHOLE - GENERAL DISORDERS												
INFLUENZA-LIKE SYMPTOMS	26(11.8)	26	10( 2.9)	12	9( 2.9)	12	30(13.8)	31	4( 2.4)	5	1( 0.6)	1
RESPIRATORY SYSTEM DISORDERS												
UPPER RESP TRACT INFECTION	24(10.9)	32	46(13.5)	59	39(12.6)	42	31(14.2)	35	16( 9.8)	17	16(10.1)	18
CENTR & PERIPH NERVOUS SYSTEM DISORDER												
HEADACHE	25(11.3)	30	31( 9.1)	47	20( 6.5)	22	24(11.0)	34	15( 9.1)	33	15( 9.5)	18
GASTRO-INTESTINAL SYSTEM DISORDERS												
DIARRHOEA	8( 3.6)	9	2( 0.6)	3	31(10.0)	37	10( 4.6)	10	8( 4.9)	8	18(11.4)	22

The vast majority of the AE's were classified as mild in severity. The only severe events reported in more than 1% of the subjects were coughing, myocardial infarction, cardiac failure and hypoglycaemic episodes. The overall AE profile in type 2 diabetes was comparable between the insulin detemir group and the NPH group. The only AE reported as more frequent in the NPH group was gastroenteritis.

*Hypoglycaemic episodes:* See clinical efficacy section

*Body weight:* See clinical efficacy section

*Cardiovascular disorders:* A meta-analysis addressing cardiovascular events across the insulin detemir trials was performed. A total of 3066 subjects from the 8 confirmatory trials were included in this analysis. The overall incidence of cardiovascular events was 7.1% in all subjects treated with insulin detemir, and was 7.9% in NPH insulin treated subjects. Among subjects with type 2 diabetes, the incidence of cardiovascular adverse events was 10.7% in the insulin detemir group and was 11.3% in the NPH insulin group. The difference was not significant.

*Injection site reactions:* Injection site reactions were reported infrequently in both treatment groups, although there was a slightly higher percentage of injection site reactions in the insulin detemir group than in the NPH insulin group (IDet: 1.7% and NPH: 0.8%) with most of the imbalance from type 1 subjects (IDet: 20/1575, 1.3% and NPH: 2/887, 0.2%) as compared to type 2 subjects (IDet: 21/871, 2.4% and NPH: 9/540, 1.7%). The events were predominantly mild (only three were moderate) and none were severe. Six subjects withdrew due to their injection site reactions: three with type 1 and three with type 2 diabetes, all were treated with insulin detemir.

### **Serious adverse events and deaths**

The frequency of serious adverse events (SAEs) in the patients with type 1 diabetes was 5.8% in total and evenly distributed among the insulin detemir and NPH insulin groups. The only SAEs reported in more than 1% of the subjects were related to glycaemic control (hypoglycaemia). Less than 2% of the subjects in either treatment group had SAEs considered probably or possibly related to the trial medication.

The frequency of SAEs in patients with type 2 diabetes was 6.7% in total and similarly distributed across the 2 treatment groups. SAEs reported in more than 1% of the subjects were: coronary events (angina pectoris, myocardial infarction), neoplasms, hypoglycaemia. Only the cases of hypoglycaemia were considered related to the trial medication.

In total, 13 deaths occurred during the insulin detemir development programme. Eight of these events involved subjects currently treated with insulin detemir, 3 deaths occurred in subjects who had ended insulin detemir treatment, and 2 deaths occurred in subjects currently treated with NPH insulin. Nine of the 11 deaths in the insulin detemir group were subjects with underlying chronic diseases as cardiovascular disease, cerebrovascular disease, malignant disease, myeloproliferative disorder, hypertension and dyslipidaemia. The deaths were in these cases most likely related to or directly caused by these diseases. In two cases, sudden deaths in young individuals were observed with no obvious explanation. The number of deaths and the mortality rates are in accordance with previous epidemiological data in diabetes populations.

#### Discontinuation due to adverse events

The incidence of adverse events leading to withdrawal was low in all trials during the clinical development programme. There was no difference in the reasons for withdrawal between treatment groups, except that slightly more subjects with type 2 diabetes treated with insulin detemir as monotherapy withdrew due to ineffective therapy in the intermediate and long-term trials as compared to the subjects treated with NPH insulin as monotherapy.

In the intermediate and long-term trials, less than 2% of the subjects with type 1 diabetes in either treatment group withdrew due to adverse events (23 subjects in the insulin detemir group and five subjects in the NPH insulin group). For subjects with type 2 diabetes less than 4% in either treatment group withdrew due to adverse events (25 subjects in the insulin detemir group and seven subjects in the NPH insulin group). No difference in withdrawals due to adverse events was evident between the insulin detemir and the NPH insulin groups, and there was no pattern in the reasons for withdrawal.

#### Laboratory findings

Clinical laboratory values were measured in all trials and included the following measurements: haemoglobin (hematocrit and erythrocytes were also performed in one trial), leucocytes (differential count if leucocytes were abnormal), thrombocytes, sodium, potassium, alkaline phosphatase, alanine aminotransferase (ALAT), lactate dehydrogenase (LDH), creatinine, total protein, albumin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low density lipoprotein (VLDL), triglycerides and free fatty acids. For one trial, measurements of gamma glutamyl transferase and total bilirubin were also performed.

The incidence of potentially clinically significant laboratory values (PCS) was 0.7% in subjects with type 1 diabetes and 7.6% in subjects with type 2 diabetes. The most frequent PCS value in subjects with type 2 diabetes was high triglyceride levels. As regards change of PCS values from baseline to end of treatment, a few differences between insulin detemir and NPH insulin in subjects with type 1 or 2 diabetes were found. None of these small differences were found consistent across all trial groups and was therefore assessed to be without clinical relevance. The incidence of PCS values did not differ between the treatment groups for subjects with type 1 as well as for type 2 diabetes.

No differences in the proportion of subjects experiencing changes from normal to abnormal ECG, or vice versa, were observed between insulin detemir and NPH insulin treated subjects with type 1 diabetes or type 2 diabetes.

The proportion of subjects experiencing changes from normal to abnormal funduscopy/fundus-photography, or vice versa, was similar between insulin detemir and NPH insulin treated subjects.

#### Immunological events

An increase in insulin detemir specific antibodies was observed after 6 months (trial 1335) and 12 months (trials 1181/1243) of treatment. No data beyond this time was available. This increase was however expected in introducing a new insulin analogue and data suggest that the increase in antibodies have no or very little impact on glycaemic control. Long-term (beyond 12 months) data on development of antibodies and their consequences for the efficacy and safety of the product should be submitted post-marketing.

### Safety in special populations

A meta-analysis addressing cardiovascular events across the insulin detemir trials was performed. A total of 3066 subjects from the 8 confirmatory trials were included in this analysis. The overall incidence of cardiovascular events was 7.1% in all subjects treated with insulin detemir, and was 7.9% in NPH treated subjects. Among subjects with type 2 diabetes, the incidence of cardiovascular adverse events was 10.7% in the insulin detemir group and was 11.3% in the NPH insulin group. The difference was not significant.

### Discussion on clinical safety

The safety parameters were derived from studies including in total 3159 subjects exposed to insulin detemir: 388 healthy subjects, 1782 patients with type 1 diabetes and 989 patients with type 2 diabetes. A total of 1248 subject years of exposure to insulin detemir were evaluated, the vast majority (98%) were derived from the 10 confirmatory intermediate (4-6 months) and long-term trials (12 months). In total, 1732 subjects were exposed to insulin detemir for 6 months or more.

Overall, the studies showed that insulin detemir was well tolerated and that the safety profile was comparable to NPH insulin. There was no noteworthy difference in frequency and incidence of adverse events, or serious adverse events with insulin detemir compared to NPH insulin, except for local reactions. The number of deaths was higher among patients currently or recently treated with insulin detemir than NPH insulin, but the deaths were apparently unlikely to be connected to the treatment.

Injection site reactions were approximately twice as common with insulin detemir as with NPH insulin. However the majority of these reactions were mild, there were no severe local reactions reported.

Overall, the frequency of major as well as minor hypoglycaemic episodes was comparable in insulin detemir and NPH insulin treatment groups, and the overall risk of having a hypoglycaemic episode was not different.

An unexpected, but very consistent finding was subjects treated with insulin detemir maintained body weight or had slight weight reductions, while subjects treated with NPH insulin tended to gain weight during the trials. This phenomenon was observed in 10 of 10 trials, and remains unexplained.

An increase in insulin detemir specific and cross-reacting antibodies was observed during insulin detemir treatment as expected. This increase was not apparently linked to adverse events or allergic reactions in the observation period. However, the number of patients exposed during 12 months is limited. Post marketing monitoring and detection of any clinical impact should follow up this finding.

## **5 Overall conclusions, benefit/risk assessment and recommendation**

### **Quality**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Viral safety and batch-to-batch consistency has been documented and the relevant tests will be performed according to the agreed specifications.

### **Preclinical pharmacology and toxicology**

Overall, the primary pharmacodynamic studies provided adequate evidence that Insulin detemir binds to insulin receptors with approximately 25% affinity compared to human insulin and activate the insulin receptor to the same extent as human insulin.

Overall, the toxicology programme revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity to reproduction.

Current data on mitogenicity does not raise particular concern but full report on the ongoing 26-week proliferation study should be submitted as a follow-up measure. Nevertheless, it should be noted that a

CPMP member would have preferred the full report on the antiproliferative study in mammary glands in rats to be performed before the granting of an Opinion.

### **Efficacy**

Levemir is a soluble long-acting insulin analogue to be used as basal insulin in combination with meal-related short- or rapid- acting insulin.

For type 1 diabetic patients insulin detemir is as efficacious as NPH insulin after 4-6 months of treatment when given as basal injection 1 to 2 times daily. Long-term efficacy data are limited to an early preparation (1200 nmol/ml) and are prone to bias due to the design of the extension studies.

For type 2 diabetic patients, insulin detemir was as good as NPH insulin if given with bolus injections with short acting insulin. Combination with metformin or monotherapy did not meet the non-inferiority criterion.

Mixing of rapid acting insulin with Levemir should be avoided because the profile of action of one or both component will change.

No clinical meaningful differences in any of the sub population were found for efficacy or safety. However, the number of patients with low serum albumin was small and therefore caution should be recommended in patients with severe hypoalbuminaemia.

No clinical studies were performed in the paediatric population but one trial in children and adolescents with type 1 diabetes was currently in progress. The applicant committed to supply data on clinical efficacy and safety in children and adolescents, after marketing authorisation.

### **Safety**

Overall, the clinical studies showed that insulin detemir was well tolerated and that the safety profile was comparable with NPH insulin. There was no noteworthy difference in adverse events with insulin detemir compared to NPH insulin, except for local reactions. Injection site reactions were approximately twice as common with insulin detemir but were usually mild. The frequency of major as well as minor hypoglycaemic episodes was comparable in insulin detemir and NPH treatment groups. Treatment with Levemir is not associated with undesirable weight gain, while subjects treated with NPH insulin tended to gain weight during the trials. This phenomenon remains unexplained.

An increase in insulin detemir specific and cross-reacting antibodies was observed during insulin detemir treatment as expected. This increase was not apparently linked to adverse events or allergic reactions in the observation period. The company will provide, in post-marketing, long term data on the development of insulin detemir antibodies and the impact of these antibodies on the safety and efficacy of insulin detemir.

### **Benefit/risk assessment**

Insulin detemir, the active ingredient in Levemir, is an insulin analogue with a prolonged duration of action based on the deletion of the amino acid threonine in position B30 of the human insulin molecule and addition of a myristic fatty acid to the  $\epsilon$ -amino group of amino acid lysine B29.

The toxicology programme revealed no special hazard for humans. Receptor affinity data and *in-vitro* mitogenicity tests revealed no evidence of an increased mitogenic potential compared to human insulin. A full report on the ongoing 26-week proliferation study should be submitted as a follow-up measure.

Clinical data support its use as basal insulin in combination with meal-related short- or rapid- acting insulin, in type 1 and 2 diabetes.

The safety profile was comparable with NPH insulin. However injection site reactions were approximately twice more frequent with Insulin detemir but were usually mild. The frequency of hypoglycaemic episodes was comparable between Insulin detemir and NPH treatment groups. Treatment with insulin detemir was not associated with undesirable weight gain.

The observed increase in insulin detemir antibodies was not linked to adverse events or allergic reactions but long term data on the development of insulin detemir antibodies and the impact of these antibodies on the safety and efficacy of insulin detemir should be submitted as follow-up measure.

Clinical efficacy and safety data in children and adolescents were lacking and will have to be submitted in post-marketing.

**Recommendation**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk ratio of Levemir in the treatment of diabetes mellitus was favourable and therefore recommended the granting of the marketing authorisation.