### Study Registration ID-number:
NN304-3714  
**NCT00825643**

### Title of the Study
A multicentre, open label, observational 24-week study to evaluate safety of initiating insulin therapy with Levemir® (insulin detemir) once-daily in oral antidiabetic drug-treated patients with Type 2 diabetes. The SOLVE™ Study. Observational study.

### Investigator(s)
3219 investigators in 10 countries: Canada (n=336), China (n=153), Germany (n=786), Israel (n=193), Italy (n=222), Poland (n=293), Portugal (n=109), Spain (n=516), Turkey (n=250), United Kingdom (n=361)

### Study Site(s)
2817 sites in 10 countries: Canada (n=313), China (n=142), Germany (n=746), Israel (n=114), Italy (n=222), Poland (n=259), Portugal (n=109), Spain (n=301), Turkey (n=250), United Kingdom (n=361)

### Publication (Reference)
Not applicable.

### Study Period
04 FEB 2008 (first patient first visit) to 28 MAR 2011 (last patient last visit)

### Phase of Development
Non-interventional study

### Objectives
#### Primary Objective:
- To assess the incidence of serious adverse drug reactions (SADRs) including major hypoglycaemic events during 24 weeks of once-daily Levemir® treatment.

#### Secondary Objective(s):
To assess the following parameters over the 24 weeks of treatment with a once-daily basal insulin analog unless stated otherwise:
- Incidence of all adverse drug reactions (ADRs)
- Incidence of minor hypoglycaemic events during the four weeks prior to each visit
- Incidence of major hypoglycaemic events during the 12 weeks preceding each visit
- Changes in HbA1c
- Changes in fasting blood glucose (FPG) variability (measured as standard deviation of FPG)
- Changes in 7-point blood glucose profile (average of the patient’s self-monitored blood glucose [SMBG] measurements)
- Changes in body weight
- Changes in waist and hip circumference
- Changes in systolic and diastolic blood pressure
- Changes in fasting lipid profile
- Changes in use of anti-hypertensive and lipid-lowering drugs
### Methodology

This was an observational, multi-centre, open-label, prospective study planned to include a sample of at least 20,000 insulin-naïve patients with Type 2 diabetes currently receiving treatment with one or more OADs. The study was conducted in ten countries: Canada, China, Germany, Israel, Italy, Poland, Portugal, Spain, Turkey and the UK.

In Canada, Germany, Poland, Portugal and the UK patients had to be insulin-naïve at enrolment. In Italy patients had started therapy with Levemir® at any time prior to enrolment, in Turkey at any time during the last three months and in Spain patients could have started once-daily Levemir® or other basal insulin treatment any time during the four weeks prior to the study. In China and Israel, patients could be insulin-naïve at study start, or have started treatment with a basal insulin analog within 4 weeks or 2 weeks before the baseline visit, respectively. In Turkey and Spain, patients could be treated by other basal insulin analogs than Levemir® during the study period: insulin glargine in Turkey, and Insulatard®, Humulin® (NPH insulin), Humalog NPL® (NPL insulin) or Lantus® (Insulin glargine) in Spain. Finally, the minimum age of participants differed across countries and ranged between 6 and 18 years old.

For all countries, whether patients were insulin-naïve or had already started insulin before the baseline visit, the clinical decision to initiate a basal insulin analog in add-on to existing OAD therapy preceded the inclusion in the study. Levemir® (or another insulin analog in Spain and Turkey) was prescribed solely as the result of a normal clinical evaluation. Levemir® was administered once daily by subcutaneous injection.

The study lasted approximately 24 weeks. Frequency and timing of visits in the study was based on accepted clinical practice for type 2 diabetes management. Data was collected in a three routinely scheduled clinic visits: Baseline visit; Interim visit (about 12 weeks after the baseline); Final visit (about 24 weeks after the baseline visit). At each visit, the physician collected information from patient recall, the patient’s notes (medical record) and the patient’s self-monitored blood glucose diary (if kept). Given the observational nature of the study, there were no study-prescribed procedures; all procedures ordered during this study were those characteristic of the routine clinical care delivered to the patient at the discretion of the participating physician.

Data collected differed in the UK and in the other nine countries. The following describes the data collected in all countries except the UK.

At the baseline visit, following the decision to include a patient in the study and after the patient provided informed consent the physician recorded the following data in the case report form:

- **Demographics:** date of birth, gender, ethnicity
- **Physical examination:** height, weight, waist and hip circumference, systolic and diastolic blood pressure
- **Medical history:** myocardial infarction, angina pectoris, neuropathy, retinopathy, nephropathy, cerebrovascular accident, transient ischemic attack, coronary artery bypass graft, angioplasty, peripheral vascular disease
Diabetes history: duration of type 2 diabetes and of OAD treatment

Treatment by anti-hypertensive or lipid-lowering drugs (yes/no)

Prior OAD therapy: type of medication (biguanides, glinides, alpha-glucosidase inhibitors, sulphonylureas, thiazolinediones, DPP-IV inhibitor, other) and dose

Latest value of HBA1c; three more recent (within 4 weeks prior to baseline visit) values of fasting blood glucose (FPG) and of 7-point self-monitored blood glucose (SMBG) profiles, that is, at pre-breakfast, post-breakfast, pre-lunch, post-lunch, pre-dinner, post-dinner and bedtime (from the patient’s notes and/or self-monitored blood glucose diary). Dates of assessments were recorded.

Most recent lipid profile (value and date of assessments)

Number and timing (daytime, night time) of minor hypoglycaemic events under current therapy over 4 weeks before the baseline visit, respectively

Number and timing (daytime, night time) of major hypoglycaemic events under current therapy over 12 weeks before the baseline visit, respectively.

In countries where the patients were not insulin-naïve at the baseline visit, physical measurements, OAD therapy, latest HBA1c, three latest FPG and 7-point self-monitored blood glucose profile values (within prior 4 weeks), lipid profile, and minor (within prior 4 weeks) and major (within prior 12 weeks) hypoglycaemic events were also recorded before insulin initiation.

At the baseline visit, the physician determined the once-daily starting dose of the basal insulin analog and timing of administration (before breakfast, before lunch, or bedtime), as well as type and dose of OADs to be used from baseline visit onwards. Where the patient had already started insulin therapy at the baseline visit, the physician recorded the start date and dose, and the dose and timing of administration recommended from baseline onwards.

During the course of the study, alterations of dose and time of administration were made at the discretion of the treating physician as long as the insulin was administered once daily; if the insulin had to be administered twice daily the patient had to be withdrawn from the study. The type, frequency and dosing of OADs could be modified at the discretion of the physician.

The following data was captured at the interim and final visits:

- Reason for study discontinuation, where relevant
- Weight, waist circumference, hip circumference, systolic and diastolic blood pressure
- Treatment by anti-hypertensive and lipid-lowering drugs (yes/no)
- Current OAD therapy: type of medication and dose
- Insulin therapy:
  - Current dose, frequency and timing of administration
  - Number of dose adjustments since last visit
  - Guidelines used for dose adjustment,
  - Number of visits and telephone contacts since last visit in relation to insulin dose adjustments
- Date and value of the most recent HbA1c (from patient’s chart)
- Date and value of the three last FPG values (within four weeks prior to the visit)
- Date and value of the three last 7-point self-measured blood glucose profiles (within four weeks prior to the visit)
- Fasting lipid profile including total cholesterol (TC), LDL-cholesterol, HDL-cholesterol and triglycerides (TG), at final visit only
- Number and timing (daytime, night time) of minor hypoglycaemic events experienced over the previous 4 weeks
- Number and timing (daytime, night time) of major hypoglycaemic events experienced over the previous 12 weeks
- Adverse drug reactions (ADR) since last visit, excluding minor hypoglycaemic events
- Serious adverse drug reactions (SADR) since last visit, including major hypoglycaemic events
- Medical events of special interest (MESI) and cases of pregnancy and their follow-up

At the baseline and final visits, the physician filled the Physician Resource Utilisation Questionnaire, and patients were invited to complete the ITAS (Insulin Treatment Appraisal Scale) questionnaire; the latter questionnaire was optional.

As mentioned previously, the data collected differed in the UK. Some clinical assessments (7-point glucose profile, lipid profile, anti-hypertensive and lipid lowering treatment, waist and hip measurements, blood pressure measurements at every visits and FPG at baseline visit) were not performed in the UK. In other countries, at least two records of OAD therapy were provided at the baseline visit: prior therapy and treatment regimen prescribed from baseline onwards. In the UK, the latter set was not recorded. In the UK the use of guidelines was assessed in regard to target glucose values, while in the other countries, the use of guidelines was assessed with respect to changes in insulin dose.

In all countries except the UK, major hypoglycaemic events were collected in the CRF over 12 weeks 4 weeks preceding insulin initiation and/or baseline visit, interim and final visit. In the UK, major hypoglycaemic events were to be notified as serious adverse events during the whole study period, however minor and major hypoglycaemic episodes were recorded in the CRF over 4 weeks preceding each visit. In the UK, all adverse events (AE) were recorded, whereas in other countries only ADR and SADR have been collected. Physician Resource Utilisation and ITAS questionnaires were not administered in the UK.

In the UK, patient satisfaction was assessed at interim and final visit by the Patient Treatment Satisfaction Questionnaire (PTSQ). A questionnaire to assess patients depressive feelings (Patient Health Questionnaire-9: PHQ-9) was administered in Poland and Israel only.

### Number of Participants Planned and Analyzed

Planned: 20000 patients  
Enrolled: 18481 patients, of which 17633 patients on Levemir®  
Analyzed: FAS (Full Analysis Set): 17374 patients; EAS (Efficacy Analysis Set): 13767; QLAS (Quality of Life Analysis Set): 6875 patients.

### Diagnosis and Main Criteria for Inclusion

All patients had type 2 diabetes and were treated with diet, exercise and one or more OADs.  
Selection of patients was at the discretion of the treating physician after the decision to prescribe the study product to the patient. Attention had to be paid to the drug interactions listed on the
The countries were divided in 5 groups, depending on whether patients were insulin naïve at time of recruitment, and on whether other basal insulins than Levemir® were allowed during the study.

**Patients insulin naïve at study start (Canada, Germany, Poland and Portugal)**

After the participating physician’s decision has been made to initiate once-daily Levemir® therapy, any patient with Type 2 diabetes who was currently treated with diet, exercise and one or more OADs could be offered to participate. Levemir® once-daily was added to existing OAD therapy from the baseline visit onwards.

**Patients insulin naïve at study start, possible retrospective inclusion (UK)**

In the UK, patients who met the eligibility criteria up to three months prior to the date of the local regulatory approval in each site could be included retrospectively. The data relating to these patients were to be transcribed from the patient’s medical records to the CRF, with the date of the patient’s insulin initiation set as the date of their baseline visit. The follow-up and final visit dates for such patients were to be considered as 12 and 24 weeks after the date of the baseline visit.

**Patients insulin naïve or recently initiated on insulin at study start (China and Israel)**

In China, patients could have initiated Levemir® as part of intensive insulin therapy (basal-bolus and less than 4 weeks therapy) in accordance with local practice prior to recruitment. They were switched from the baseline visit onwards to once daily Levemir® combined with one or more OADs. Both initiation of Levemir® and inclusion in the study were at the physician’s discretion.

In Israel, patients could be included in the study within two weeks of initiation of Levemir® in combination with one or more OADs.

**Patients insulin initiated at study start, no other insulin allowed (Italy)**

In Italy, any patient with Type 2 diabetes who was currently treated with once-daily Levemir® in combination with OADs could be offered to participate. Levemir® could have been initiated any time before inclusion in the study.

**Patients insulin initiated at study start, other insulins allowed (Turkey, Spain)**

In Turkey, any patient with Type 2 diabetes who was currently treated with diet, exercise, one or more OADs and a basal insulin analogue (initiated within the last three months) could be offered to participate. Two basal insulin analogues could be used before and during the study: Levemir® [insulin detemir] or Lantus® [Insulin glargine].

In Spain, any patient with Type 2 diabetes who during the preceding month to the beginning of the study had initiated treatment with once-daily basal insulin (Levemir® [insulin detemir], Insulatard®, Humulin® [NPH insulin], Humalog NPL® [NPL insulin] or Lantus® [Insulin glargine]) and who was currently treated with diet, exercise and one or more OADs could be offered to participate. Patients could switch to another basal insulin analog during the study.

**Test Product, Dose and Mode of Administration, Batch Number**

The study product was insulin detemir (Levemir) which was administered subcutaneously once daily. The dose was determined according to the insulin analog monograph. Patients obtained insulin detemir from the retail pharmacy.

**Duration of Treatment**

24 weeks.
Criteria for Evaluation - Effectiveness

The primary study variable was a safety endpoint: incidence of SADRs including major hypoglycaemic events during 24 weeks of once-daily basal insulin analog treatment.

The secondary efficacy endpoints to be assessed in this study included: HbA1c, mean FPG per subject, variability of the different FPG values per subject, 7-point blood glucose profile (including assessment at pre-breakfast, post-breakfast, pre-lunch, post-lunch, pre-dinner, post-dinner, and night), lipid profile (TC, HDL-C, LDL-C and TG), and proportion of patients using anti-hypertensive and lipid-lowering drugs.

The analyses of (secondary) efficacy endpoints were performed on the EAS for the total cohort. Absolute change from baseline in HbA1c, mean FPG, FPG variability, mean SMBG, TC, LDL, HDL, and TG were calculated as value at interim or final visit minus the value at baseline. Absolute change at a given time point (interim or final visit) was calculated only if both a baseline and time point measurements were available.

The following items were displayed in tables:

**HbA1c**

- HbA1c descriptive statistics at each visit (pre-insulin, baseline, interim and final visits), including the absolute change from pre-insulin value at interim and final visits
- Descriptive statistics for time span between date of pre-insulin HbA1c measurement and baseline, interim and final visit dates
- Frequency of HbA1c values at pre-insulin and final visits considering 0.5% intervals
- Proportion of subjects with pre-insulin HbA1c levels in the following categories:
  - HbA1c < 9% and HbA1c ≥ 9%
  - HbA1c ≤ 6.5%; 6.5% < HbA1c ≤ 7.5% and HbA1c > 7.5%
- Frequencies for time span between date of pre-insulin HbA1c measurement and insulin initiation considering the following intervals:
  - 0 weeks
  - 0-2 weeks
  - >3-<=4 weeks
  - >1-<=3 months
  - >3-<=6 months
  - >6 months
- Proportion of subjects with final HbA1c levels in the following categories:
  - HbA1c < 9% and HbA1c ≥ 9%
  - HbA1c ≤ 6.5%; 6.5% < HbA1c ≤ 7.5% and HbA1c > 7.5%
- Proportion of subjects achieving HbA1c < 7.0% at the final visit
- Proportion of subjects achieving HbA1c < 6.5% at end of study with or without hypoglycaemic episode during the study period
- Proportion of subjects achieving HbA1c < 6.5% at end of study with or without hypoglycaemic episode during the study period
**FPG**
- Mean FPG descriptive statistics at each visit (pre-insulin, baseline, interim and final visits), including the absolute change from pre-insulin value at interim and final visits
- FPG variability descriptive statistics (pre-insulin, baseline, interim and final visits), including the absolute change from pre-insulin value at interim and final visits
- Frequency of mean FPG at baseline and final visit considering 2 mmol/L intervals

**Blood glucose profile**
- SMBG descriptive statistics by time at each visit (pre-insulin, baseline, interim and final visits), including the absolute change from pre-insulin value at interim and final visits
- Frequencies of SMBG by time point at pre-insulin assessment and final visit considering 2 mmol/L intervals

**Lipid profile**
- TC, HDL, LDL, and TG descriptive statistics at pre-insulin, baseline, and final visits, including the absolute change from pre-insulin values
- TC, HDL, LDL and TG frequencies considering 1 mmol/L intervals at pre-insulin assessment and final visit (values >10 mmol/l will be categorized into a single interval)
- Proportion of subjects reporting use of any lipid-lowering drugs at each visit
- Proportion of subjects reporting use of lipid-lowering and antihypertensive drugs at pre-insulin, baseline and final visits.

Aggregated tables were produced for the total cohort and for subgroups defined (only those categories with >0 patients were to be considered for the subgroups). The following variables were summarized in aggregated tables:
- HbA1c descriptive statistics at each visit, including the absolute change from pre-insulin values to final visit
- Proportion of subjects achieving HbA1c < 6.5% and < 7.0% at end of study
- Proportion of subjects achieving HbA1c < 6.5% and < 7.0% at end of study with or without hypoglycaemia
- Mean FPG descriptive statistics at each visit, including the absolute change from pre-insulin values to final visit
- TC, LDL, HDL and TG descriptive statistics at each visit, including the absolute change from pre-insulin values to final visit.

**Criteria for Evaluation - Safety**
The primary study variable was a safety endpoint: incidence of SADRs including major hypoglycaemic events during 24 weeks of once-daily Le vemir® treatment.
The secondary safety endpoints to be displayed in tables were:

**ADRs/SADRs**
- Number of SADRs and summary table of severity, relationship to study product, outcome and action taken for ADRs
• Number of SADRs, number and percentages of patients with SADRs in total and per system organ class and preferred term
• Number of non-serious ADRs and summary table of severity, relationship to study product, outcome and action taken for ADRs
• Number of non-serious ADRs, number and percentages of patients with ADRs in total and per system organ class and preferred term

**Hypoglycaemic events**

• Incidence of minor and major overall, daytime and nocturnal hypoglycaemic events at pre-insulin, baseline, interim and final visits
• Descriptive statistics for number of major overall, daytime and nocturnal events per patient year at pre-insulin, interim and final visits including changes from pre-insulin period to final visit
• Descriptive statistics for absolute number of major overall, daytime and nocturnal events at pre-insulin, baseline, interim, and final visits including change from pre-insulin period at interim and final visits
• Descriptive statistics for number of minor overall, daytime and nocturnal events per patient year at pre-insulin, interim and final visits including changes from pre-insulin period to interim and final visit
• Descriptive statistics for absolute number of minor overall, daytime and nocturnal events at pre-insulin, baseline, interim, and final visits including change from pre-insulin period at interim and final visits.

**Physical measurements**

• Weight and BMI descriptive statistics at pre-insulin, baseline, interim and final visits, including the absolute change from pre-insulin assessment at interim and final visits
• Waist circumference descriptive statistics at pre-insulin, baseline, interim and final visits, including the absolute change from pre-insulin assessment at interim and final visits
• Hip circumference descriptive statistics at pre-insulin, baseline, interim and final visits, including the absolute change from pre-insulin assessment at interim and final visits
• Waist: hip ratio descriptive statistics at pre-insulin, baseline, interim and final visits, including the absolute change from pre-insulin assessment at interim and final visits
• Systolic and Diastolic blood pressure descriptive statistics at pre-insulin, baseline, interim and final visits, including the absolute change from pre-insulin assessment at interim and final visits.

Aggregated tables were produced for the total cohort and for subgroups (only those categories with >0 patients were to be considered). The following variables were summarized in aggregated tables:

• Body weight descriptive statistics at each visit, including the absolute change from pre-insulin assessment at final visit.
• Frequency of subjects with the following weight changes from pre-insulin assessment at interim and final visits:
• > -1 kg (weight loss of more than 1 kg)
• [-1 to 1 kg] (within ± 1 kg of the pre-insulin weight)
• > +1 kg (weight gain of more than 1 kg)

- Systolic and Diastolic blood pressure descriptive statistics at each visit, including the absolute change from pre-insulin assessment at final visit.
- Incidence of minor / major hypoglycaemic events in the 4 / 12 weeks preceding the baseline, interim and final visits
- Number of total minor / daytime minor / nocturnal minor hypoglycaemic events per patient year
- Number of total major / daytime major / nocturnal major hypoglycaemic events per patient year
- Number of subjects with at least one non-serious ADR and total number of non-serious ADRs
- Number of subjects with at least one SADR and total number of SADRs.

**Statistical Methods**

Continuous variables were summarized with descriptive statistics (total number of observations with available values (N), number of observation with missing values (Nmiss), Mean, standard deviation (SD), Minimum (Min), Maximum (Max), Median, 1st quartile (Q1), 3rd quartile (Q3), and 95% Confidence Interval (CI) of the mean).

Categorical data were summarized with the number (N) and percentage (%) of subjects in each category. Missing observations were presented in tables as a separate category. The calculation of percentages did not include the missing category. When continuous variables were tabulated using intervals, cumulative percentages were also displayed.

Statistical testing/comparison of data before and after basal insulin analog therapy were performed with paired t-tests for continuous variables such as weight, HbA1c, or mean FPG, with Wilcoxon test for ordinal categorical variables and with McNemar test for discrete variables such as incidence of hypoglycaemic events.

The influence of predictor variables on the change in outcome variables was evaluated with multivariate linear regression models for continuous outcome variables and logistic models for discrete/binary outcome variables.

All testing used two-sided tests at α= 0.05 level of significance. All results were interpreted in a descriptive manner. As already stated, missing data were not replaced.

Three different analysis populations were defined in this study:
- Full Analysis Set (FAS)
- Effectiveness Analysis Set (EAS)
- Quality of Life Analysis Set (QLAS).

The definition of each analysis population differed across countries as listed in the table below.
### Full Analysis Set (FAS)

<table>
<thead>
<tr>
<th>Country</th>
<th>Full Analysis Set (FAS)</th>
<th>Efficacy Analysis Set (EAS)</th>
<th>Quality of Life Analysis Set (QLAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>All enrolled patients who have been prescribed basal insulin at baseline (i.e. dosage &gt; 0 IU). The enrolment will be defined as the answer Yes to the question “Have you obtained informed consent for this patient?” or an available date of informed consent.</td>
<td>All patients from FAS who have a final visit, at least one measurement concerning FPG, most recent HbA1c, weight or hypoglycaemic events (Yes, No) at baseline and final visit, and a follow up time of at least 16 weeks to not more than 32 weeks.</td>
<td>All patients from FAS who have completed at least one item of the ITAS questionnaire at baseline and final visit or (where applicable *) at least one item of the PHQ-9 questionnaire at baseline and final visit</td>
</tr>
<tr>
<td>China</td>
<td>All enrolled patients who have been prescribed Levemir® during the study period (i.e. dosage &gt; 0 IU) and reported safety information either at a clinic visit or by telephone. The enrolment will be defined by any available data in the baseline CRF. Safety information is any entry regarding hypoglycaemic episodes, adverse events or weight at the interim or final visit.</td>
<td>All patients from FAS who have supplied efficacy data, that is, who provided HbA1c measurement at baseline and at least one post-baseline visit (interim and/or final).</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Germany</td>
<td>All enrolled patients who have been prescribed basal insulin at baseline (i.e. dosage &gt; 0 IU). The enrolment will be defined as the answer Yes to the question “Have you obtained informed consent for this patient?” or an available date of informed consent.</td>
<td>All patients from FAS who have a final visit, at least one measurement concerning FPG, most recent HbA1c, weight or hypoglycaemic events (Yes, No) at baseline and final visit, and a follow up time of at least 16 weeks to not more than 32 weeks.</td>
<td>All patients from FAS who have completed at least one item of the ITAS questionnaire at baseline and final visit or (where applicable *) at least one item of the PHQ-9 questionnaire at baseline and final visit</td>
</tr>
<tr>
<td>Israel</td>
<td>All enrolled patients who have been prescribed basal insulin at baseline (i.e. dosage &gt; 0 IU). The enrolment will be defined as the answer Yes to the question “Have you obtained informed consent for this patient?” or an available date of informed consent.</td>
<td>All patients from FAS who have a final visit, at least one measurement concerning FPG, most recent HbA1c, weight or hypoglycaemic events (Yes, No) at baseline and final visit, and a follow up time of at least 16 weeks to not more than 32 weeks.</td>
<td>All patients from FAS who have completed at least one item of the ITAS questionnaire at baseline and final visit or (where applicable *) at least one item of the PHQ-9 questionnaire at baseline and final visit</td>
</tr>
<tr>
<td>Italy</td>
<td>All enrolled patients who have been prescribed basal insulin at baseline (i.e. dosage &gt; 0 IU). The enrolment will be defined as the answer Yes to the question “Have you obtained informed consent for this patient?” or an available date of informed consent.</td>
<td>All patients from FAS who have a final visit, at least one measurement concerning FPG, most recent HbA1c, weight or hypoglycaemic events (Yes, No) at baseline and final visit, and a follow up time of at least 16 weeks to not more than 32 weeks.</td>
<td>All patients from FAS who have completed at least one item of the ITAS questionnaire at baseline and final visit or (where applicable *) at least one item of the PHQ-9 questionnaire at baseline and final visit</td>
</tr>
<tr>
<td>Poland</td>
<td>All enrolled patients who have been prescribed basal insulin at baseline (i.e. dosage &gt; 0 IU). The enrolment will be defined as the answer Yes to the question “Have you obtained informed consent for this patient?” or an available date of informed consent.</td>
<td>All patients from FAS who have a final visit, at least one measurement concerning FPG, most recent HbA1c, weight or hypoglycaemic events (Yes, No) at baseline and final visit, and a follow up time of at least 16 weeks to not more than 32 weeks.</td>
<td>All patients from FAS who have completed at least one item of the ITAS questionnaire at baseline and final visit or (where applicable *) at least one item of the PHQ-9 questionnaire at baseline and final visit</td>
</tr>
<tr>
<td>Portugal</td>
<td>All enrolled patients who have been prescribed basal insulin at baseline (i.e. dosage &gt; 0 IU). The enrolment will be defined as the answer Yes to the question “Have you obtained informed consent for this patient?” or an available date of informed consent.</td>
<td>All patients from FAS who have a final visit, at least one measurement concerning FPG, most recent HbA1c, weight or hypoglycaemic events (Yes, No) at baseline and final visit, and a follow up time of at least 16 weeks to not more than 32 weeks.</td>
<td>All patients from FAS who have completed at least one item of the ITAS questionnaire at baseline and final visit or (where applicable *) at least one item of the PHQ-9 questionnaire at baseline and final visit</td>
</tr>
<tr>
<td>Spain</td>
<td>All enrolled patients who have been prescribed basal insulin at baseline (i.e. dosage &gt; 0 IU). The enrolment will be defined as the answer Yes to the question “Have you obtained informed consent for this patient?” or an available date of informed consent.</td>
<td>All patients from FAS who have a final visit, at least one measurement concerning FPG, most recent HbA1c, weight or hypoglycaemic events (Yes, No) at baseline and final visit, and a follow up time of at least 16 weeks to not more than 32 weeks.</td>
<td>All patients from FAS who have completed at least one item of the ITAS questionnaire at baseline and final visit or (where applicable *) at least one item of the PHQ-9 questionnaire at baseline and final visit</td>
</tr>
<tr>
<td>Turkey</td>
<td>All enrolled patients who have been prescribed basal insulin at baseline (i.e. dosage &gt; 0 IU). The enrolment will be defined as the answer Yes to the question “Have you obtained informed consent for this patient?” or an available date of informed consent.</td>
<td>All patients from FAS who have a final visit, at least one measurement concerning FPG, most recent HbA1c, weight or hypoglycaemic events (Yes, No) at baseline and final visit, and a follow up time of at least 16 weeks to not more than 32 weeks.</td>
<td>All patients from FAS who have completed at least one item of the ITAS questionnaire at baseline and final visit or (where applicable *) at least one item of the PHQ-9 questionnaire at baseline and final visit</td>
</tr>
<tr>
<td>UK</td>
<td>All enrolled patients who have been prescribed Levemir® during the study period (i.e. dosage &gt; 0 IU) and reported safety information either at a clinic visit or by telephone. The enrolment will be defined by any available data in the baseline CRF. Safety information is any entry regarding hypoglycaemic episodes, adverse events or weight at the interim or final visit.</td>
<td>All patients from FAS who have supplied efficacy data, that is, who provided HbA1c measurement at baseline and at least one post-baseline visit (interim and/or final).</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>

*PHQ-9 was collected in Israel and Poland only

For the global analysis, the following groups and subgroups were defined:

- **Total cohort**
- **Pre-insulin OAD therapy:**
  - 1 OAD
  - 2 OAD
  - > 2 OADs
- **Therapy adherence (patients who were on the same OAD(s) at pre-insulin assessment, insulin initiation and final visit):**
  - Biguanides only -> Insulin + Biguanides only
  - Sulphonylyreas alone -> Insulin + Sulphonylyreas alone
  - Biguanides and Sulphonylyreas -> Insulin + Biguanides and Sulphonylyreas
- **Age:** < 75 and ≥ 75 years
- **Patients with or without macrovascular complications at baseline**
- **Pre-insulin HbA1c:** < 7.6%; 7.6-9.0%; ≤ 9.0% and > 9.0%
- **Patients with or without any hypoglycaemic episodes during the study**
- **Patients with or without any hypoglycaemic episodes before insulin initiation.**
- **Pre-insulin BMI category:** BMI < 25, 25-30, 30-35, BMI < 35 and BMI ≥ 35 kg/m²
- **Patients using pre-insulin DPP-IV therapy, alone or in combination:**
  - DPP-IV at pre-insulin -> Insulin with DPP-IV at insulin initiation
  - DPP-IV at pre-insulin -> Insulin without DPP-IV at insulin initiation
• Duration of diabetes at study start: < 5 years; 5-10 years (inclusive); > 10 years.

The analyses of baseline characteristics and safety data were performed on FAS, the analyses of the efficacy outcome variables on EAS and the analysis of resource utilisation data were based on FAS. The analysis of the QoL data was conducted for the QLAS.

Demography of Study Population
In total 18451 patients were enrolled in the study, of which 17633 were prescribed Levemir®. Of the 17633 patients who were enrolled in the study and prescribed Levemir®, 17374 patients comprised the Full Analysis Set (FAS), 13767 the Efficacy Analysis Set (EAS) and 6875 patients were included in the Quality of Life Analysis Set (QLAS).

In FAS, 52.9% (n=9189/17359) of patients were males and 47.1% (n=8170/17359) were females. The mean age was 61.6 years (SD: 11.51, n=17271). In terms of ethnicity, 74.2% (n=12253/16524) of patients were White, 0.7% (n=117/16524) were Black and 25.1% (n=4154/16524) were of Other ethnicity (including Asians).

The mean weight at baseline was 80.93 kg (SD: 17.72, n=17209) for the overall cohort (males: 85.26 kg, n=9102; women: 76.06 kg, n=8092). The mean BMI at the baseline visit was 29.26 kg/m² (n=16968) for the overall cohort (men: 28.76 kg/m², n=8990; women: 29.82 kg/m², n=7964). The mean systolic and diastolic blood pressure was 135.7 mmHg (n=13997) and 80.5 mmHg (n=13978), respectively, without difference between genders.

Patients had been diagnosed with type 2 diabetes for a mean of 9.75 years (n=17302) and had been on OAD therapy for a mean time span of 8.45 years (n=16932). Macrovascular complications were present in 26.6% (n=4542/17047) of patients and microvascular complications in 33.0% (n=5630/17280).

Effectiveness Results
Primary endpoint
The primary endpoint of this study was a safety endpoint: incidence of SADRs including major hypoglycaemic events during 24 weeks of once-daily Levemir® treatment. Conclusions on the primary endpoint are provided in the Safety Results section.

Changes in OAD therapy (FAS)
Prior to starting insulin treatment, 81.3% (n=13897/17086) of patients were treated by biguanides either alone or combined with other OADs, 59.3% (n=10140/17086) by sulphonylureas, 16.1% (n=2748/17086) by glinides, 12.2% (n=2080/17086) by α-glucosidase-inhibitors, 12.1% (n=2075/17086) by thiazolidinediones, 6.5% (n=1108/17086) were on DPP-IV (dipeptidyl peptidase IV) inhibitors, and 0.1% (n=22/17086) received other OAD.

At insulin initiation, biguanides were prescribed to 78.9% (n=12899/16346) of patients, sulphonylureas to 47.8% (n=7814/16346), glinides to 18.5% (n=3031/16346), α-glucosidase-inhibitors to 11.9% (n=1943/16346), thiazolidinediones to 8.4% (n=1371/16346), and DPP-IV inhibitors to 4.7% (n=773/16346); 8 patients (< 0.1%) received other OAD. The proportion of patients receiving each OAD varied little thereafter. Biguanides, sulphonylureas and glinides remained the most frequently prescribed OADs throughout the study follow-up.

The most frequent OAD regimen observed in association to insulin were biguanides plus
sulphonylureas (insulin initiation: 5077/16346, 31.1%; final visit: n=4102/14520, 28.3%), biguanides alone (insulin initiation: 3917/16346, 24.0%; final visit: n=3764/14520, 25.9%), and 2 OADs excluding the combination of biguanides and sulphonylureas (insulin initiation: 3073/16346, 18.8%; final visit: n=2903/14520, 20.0%).

Changes in basal insulin analog dose (FAS)
The mean dose of insulin prescribed to the overall FAS cohort was 12.70 units (n=17317) at insulin initiation, 17.09 units (n=8036) at baseline visit, 19.74 units (n=15845) at interim visit and 21.60 units (n=14909) at the final visit. These doses corresponded to 0.16 units/kg (n=17154), 0.22 units/kg (n=7922), 0.25 units/kg (n=15675), and 0.27 units/kg (n=14772) at insulin initiation, baseline, interim and final visits, respectively. The insulin dose increased over time. For patients with data on insulin dose at insulin initiation and at interim visit, the mean daily dose increased from 12.62 units at insulin initiation to 19.73 units at interim visit (change: +7.11 units, 95% CI: [6.91; 7.31] units, n=15801, p < 0.001). For patients with data on insulin dose at insulin initiation and final visit, the mean dose was 12.61 units at insulin initiation and 21.60 units at the final visit (change: +8.99 units, 95% CI: [8.75; 9.23] units, n=14868, p < 0.001). The most frequent time of insulin administration was at bedtime.

The percentage of patients with insulin dose changed was 61.9% (n=9398/15189) between baseline and interim visits, and 46.0% (n=6634/14421) between the interim and final visits. Dose changes had been performed according to local guidelines for 41.4% of patients (n=3890/9398) and 42.2% of patients (n=2797/6634), respectively. Levetiratide® SmPC were referred to in 22.1% (n=2078/9398) of patients at interim visit, and 19.4% (n=1284/6634) of patients at final visit; no guidelines were specified for 23.2% (n=2176/9398) of patients at the interim visit and for 24.6% of patients (n=1635/6634) at the final visit. For the remainder of patients, changes had been advised in accordance to “SPC” (0.3% at either visit) or other guidelines.

Changes in level of HbA1c (EAS)
HbA1c levels improved significantly over time after introduction of insulin therapy. The mean rate of HbA1c for the overall EAS cohort was 8.88% (n=11023) prior to insulin initiation, 8.53% (n=3821) at baseline visit, 7.81% (n=10984) at interim visit and 7.53% (n=11740) at final visit. For patients with data on HbA1c concentration at both time points, the mean HbA1c concentration was 8.86% at pre-insulin assessment and 7.80% at interim visit, with a statistically significant reduction of -1.06% (n=9027, p < 0.001). For patients with data on HbA1c concentration at pre-insulin assessment and at final visit, the mean value was 8.85% before insulin initiation and 7.54% at the final visit, showing a statistically significant reduction of -1.30% (n=9630, p < 0.001) between these two time points.

Prior to insulin initiation 7.4% (n=819/11023) of patients had an HbA1c level < 7.0%, whereas 32.8% (n=3850/11023) patients attending the final visit were at such level.

Changes in fasting plasma glucose (FPG) value and variability (EAS)
FPG levels improved after the introduction of insulin therapy. The mean FPG was 10.27 mmol/L (n=7326) before insulin initiation, 9.28 mmol/L (n=2778) at baseline visit, 7.53 mmol/L (n=9618) at the interim visit, and 7.24 mmol/L (n=9572) at the final visit. For patients with data on FPG prior to insulin initiation and at interim or final visit FPG level decreased significantly at interim visit with a mean change of -2.81 mmol/L (n=6252; p < 0.001), and at the final visit, with a mean change of -3.06 mmol/L (n=6251, p < 0.001).
At insulin initiation 13.1% (n=945/7236) of patients had a FPG level < 7.5 mmol/L prior to insulin initiation. At the interim and final visits, this proportion was 57.8% (n=5556/9618) and 64.9% (n=6211/9572) of patients with data, respectively.

The mean variability between the three more recent FPG measurements was 2.00 mmol/L (n=4611) prior to insulin initiation, 2.22 mmol/L (n=1978) at baseline visit, 0.97 (n=7263) at the interim visit, and 0.94 mmol/L (n=7214) at the final visit. For patients with data at the two time points, FPG variability was significantly reduced from pre-insulin assessment at interim visit (mean change: -1.04 mmol/L, n=3678, p < 0.001), and at the final visit (mean change: -0.97 mmol/L, n=3638, p < 0.001).

Changes in 7-point blood glucose profile (EAS)

Prior to insulin initiation, the mean self-assessed blood glucose level was 9.60 mmol/L (n=3296) before breakfast, 11.85 mmol/L (n=2752) post-breakfast, 9.66 mmol/L (n=2234) pre-lunch, 11.59 mmol/L (n=2640) post-lunch, 9.51 mmol/L (n=2255) pre-dinner, 11.39 mmol/L (n=2488) post-dinner, and 9.46 mmol/L (n=1611) at night. The mean blood glucose decreased significantly between the pre-insulin assessment and the final visit in patients assessable for changes at any of the time points; the mean differences observed were -2.69 mmol/L (n=2643, p < 0.001) pre-breakfast, -3.07 mmol/L (n=2165, p < 0.001) post-breakfast, -2.43 mmol/L (n=1641, p < 0.001) pre-lunch, -2.59 mmol/L (n=2035, p < 0.001), post-lunch, -2.04 mmol/L (n=1652, p<0.001) pre-dinner, -2.42 mmol/L (n=1902, p < 0.001) post-dinner, and -2.02 mmol/L (n=1161, p < 0.001) at night.

Changes in lipid profile (EAS)

The mean total cholesterol (TC) level was 5.08 mmol/L (n=8271) prior to insulin initiation and 4.76 mmol/L (n=8100) at the final visit. Patients with data before insulin initiation and at final visit had a significant reduction of TC level between these two time points (mean change: -0.30 mmol/L, n=5962, p < 0.001).

The mean HDL-C level was 1.23 mmol/L prior to insulin initiation (n=7517) and 1.25 mmol/L (n=7536) at the final visit. A very modest increase of HDL-C level by +0.01 mmol/L was observed between pre-insulin and final assessments (n=5278, p = 0.008).

The mean LDL-C level was 2.92 mmol/L (n=6995) prior to insulin initiation and 2.77 mmol/L (n=6886) at the final visit. In patients with pre-insulin and final data, a mean change of -0.16 mmol/L was observed at final visit (n=4792; p < 0.001).

The mean triglycerides level was 2.08 mmol/L (n=7932) prior to insulin initiation and 1.77 mmol/L (SD: 0.99, n=7913) at the final visit. In patients assessable for change, a reduction in TG level was observed at final visit (mean change: -0.29 mmol/L, n=5649, p < 0.001).

Lipid lowering and anti-hypertensive therapy (EAS)

The proportion of patients on lipid-lowering therapy was 43.5% (n=5193/11942) prior to initiating insulin and 46.0% (n=5259/11440) at the final visit.

The proportion of patients on anti-hypertensive therapy was 62.1% (n=7905/12731) prior to insulin initiation, 63.4% (n=7868/12414) at the interim visit and 63.2% (n=8035/12705) at the final visit.

Physician resource utilisation (FAS)

Item 1 related to training dispensed to patients at the baseline visit: 91.4% (n=15.22/16427) of
patients had received dietary advice, 75.9% (n=12469/16427) had received training on basal insulin mode of action, 88.8% (14587/16427) on how to avoid and manage hypoglycaemia, 90.2% (n=14812/16427) on how to monitor blood glucose, 76.8% (n=12615/16427) on how to self adjust the insulin dose, 89.9% (n=14775/16427) on device handling, and 10.4% (n=1707/16427) of patients had received training on other topics.

Overall, the medical staff had spent a mean time of 14.8 min (SD: 12.93, n=16194) in training the patient to self-inject insulin, 11.3 min (SD: 10.67, n=15120) in training the patient to self-adjust the insulin dose and 16.9 min (SD: 17.36, n=15880) in training the patient on other topics such as diet or blood glucose monitoring [Item 3].

The two prominent devices to be used for administration of insulin [Item 2] were FlexPen® (n=10199/16277, 62.7%) and NovoPen® 4 (n=3872/16277, 23.8%).

Convincing the patient to start therapy with a basal insulin analog [Item 4] had been either very easy for 12.0% of cases (n=1973/16426), easy for 46.0% (n=7550/16426), neither easy nor difficult for 28.0% (n=4602/16426) difficult for 11.4% (n=1878/16426), and very difficult for 2.5% (n=403/16426) of patients.

Training the patient to self-inject insulin and adjust insulin dose [Item 5] was deemed very easy for 11.1% (n=1817/16414) of patients, easy for 48.5% (n=7954/16414), neither easy nor difficult for 29.6% (n=4854/16414), difficult for 8.3% (n=1365/16414) and very difficult for 1.3% (n=207/16414) of patients.

The investigator was very confident for 16.0% (n=2632/16423) of patients, confident for 53.8% (n=8833/16423), somewhat confident for 25.0% (n=4100/16423), not confident for 3.6% (n=594/16423), and not at all confident for 0.5% (n=86/16423) of patients that they could correctly self-inject and self-adjust the dose of basal insulin analog [Item 6].

At the final visit, the investigator rated the ease of insulin management by the patient as very easy for 19.8% (n=2852/14388) of patients, easy for 58.9% (n=8468/14388), neutral for 15.8% (n=2277/14388) of patients, difficult for 4.9% (n=712/14388), and very difficult for 0.5% (n=79/14388).

The majority of investigators were very satisfied (n=3231/14325, 22.6%) or satisfied (n=7276/14325, 50.8%) with the outcome, that is, patients achieving the target HbA1c level. Investigators were neutral (that is, neither satisfied, nor dissatisfied) for 15.8% (n=2268/14325) of patients, dissatisfied for 9.5% (n=1365/14325), and very dissatisfied for 1.3% (n=185/14325) of patients, respectively.

**ITAS and PHQ-9 (QLAS)**

The mean positive items subscale score (where a higher score indicates a better appraisal) was 14.93 (n=6872) at baseline visit and 15.07 (n=6860) at the final visit. In patients assessable for change from baseline, a slight improvement of the positive items subscale score was observed at the final visit (mean change: +0.14, n=6857, p <0.001).

The mean negative items subscale score (where a lower score indicates a better appraisal) was 44.24 (n=6872) at baseline visit and 40.86 (n=6863) at the final visit. In patients assessable for change from baseline, a reduction of this score, corresponding to an improvement, was observed at the final visit (mean change: -3.38, n=6860, p <0.001).

The overall ITAS score (where a lower score indicates a better appraisal) was 53.16 (n=6872) at
the baseline visit and 49.63 (n=6863) at the final visit, with a mean reduction of -3.52 (n=6860, p < 0.001) between these two visits. For the negative items subscale and for the ITAS total score, the higher the score, the worst the appraisal; a reduction of score indicates an improvement.

The mean PHQ-9 score was 5.75 (n=850) at baseline visit and 3.43 (n=825) at the final visit. The PHQ-9 score decreased significantly between these two visits (mean change: -2.35, SD: 4.90, n=800, p < 0.001), indicating a lower severity of depressive symptoms.

Subgroup analyses
Effectiveness outcomes were similar across the different classes of Levemir® subgroups, with the exceptions detailed below.

In terms of number of OADS:

- The prominent OAD regimen for patients < 75 years of age was 2 OADs prior to insulin initiation (n=7863/14617, 53.8%) and at any other time point (initiation: n=7049/14051, 50.2%; interim: n=6609/13434, 49.2%; final: n=6113/12554, 48.7%). The prominent regimen for patients aged ≥ 75 years was a combination of 2 OADS prior to and at insulin initiation (pre-insulin: n=1341/2371, 56.6%; initiation: n=1073/2205, 48.7%), but 1 OAD at interim and final visits (interim: n=1038/2171, 47.8%; final: n=975/2015, 48.4%).

- The prominent regimen for patients with BMI < 25 kg/m² was 2 OADs prior to and at insulin initiation (pre-insulin: n=1745/3459, 50.4%; initiation: n=1541/3381, 45.6%) and 1 OAD at the interim and final visits (interim: n=1433/3197, 44.8%; final: n=1339/3015, 44.4%). In the other BMI classes it was 2 OADs at any time point.

- In patients with pre-insulin HbA1c < 7.6% the main regimen at insulin initiation (n=795/2705, 29.4%), interim (n=782/2591, 30.2%) and final visit (n=732/2460, 29.8%) was biguanides alone. In the other classes, it was a combination of biguanides and sulphonylureas. Most patients from the HbA1c < 7.6% class were on 2 OADs prior to insulin initiation, and on one OAD from insulin initiation onwards, whereas in other HbA1c classes patients remained mostly on 2 OADs at every time point.

- The majority of patients with pre-insulin DPP-IV inhibitors therapy were on combined therapy and received 2 OADs or > 2 OADs. In patients continuing DPP-IV inhibitors at insulin initiation the mean number of OADs was 2.4 prior to insulin initiation, 2.2 at insulin initiation, and 2.1 at interim and final visits. In patients discontinuing DPP-IV inhibitors, the mean number of OADs was 2.6 prior to insulin initiation and was reduced to 1.5 at insulin initiation, interim and final visits.

- In patients with pre-insulin hypoglycaemic events, the prominent OAD regimen before insulin initiation was a combination of biguanides and sulphonylureas (n=284/827, 34.3%). It was biguanides alone at insulin initiation and from this point onwards (insulin initiation: n=201/804, 25.0%; interim visit: n=187/761, 24.6%; final visit: n=185/711, 26.0%). Most patients in this class were on 2 OADs prior to insulin initiation and on 1 OAD from insulin initiation onwards. In patients without pre-insulin hypoglycaemic events, the prominent OAD regimen at every time point was a combination of biguanides and sulphonylureas; most patients received 2 OADs at every time point.

- The combination of biguanides and sulphonylureas was the prominent OAD regimen in patients with diabetes duration of 5-10 years (28.1%-35.9% across time points) and > 10 years
(33.8%-40.7% across time points), whereas it was biguanides alone in patients with diabetes duration < 5 years (27.4%-34.8% across time points). Most patients with diabetes duration < 5 years were on 2 OADs prior to insulin initiation, and on one OAD from insulin initiation onwards, whereas patients with longer diabetes duration remained mostly on 2 OADs at every time point.

In terms of insulin dosing:

- At insulin initiation the mean insulin daily dose increased in line with the BMI: 11.20 units (n=3055) for patients with BMI < 25 kg/m², 12.31 units (n=5880) for patients with BMI of 25-30 kg/m², 13.34 units (n=3587) for patients with BMI of 30-35 kg/m², and 14.17 units (n=2035) for patients with BMI ≥ 35 kg/m². The mean insulin daily dose increased throughout the study in all BMI classes, this accrual was more important for patients in the high BMI classes. The mean change in insulin daily dose observed between insulin initiation and final visit was +5.52 units (n=3055) for patients with BMI < 25 kg/m², +7.62 units (n=5880) for patients with BMI of 25-30 kg/m², +10.37 units (n=3587) for patients with BMI of 30-35 kg/m², and +15.40 units (n=2035) for patients with BMI ≥ 35 kg/m².

- At insulin initiation the mean insulin daily dose increased in line with pre-insulin HbA1c: 10.60 units (n=2516) for patients with HbA1c level < 7.6%, 11.99 units (n=4749) for patients with HbA1c level of 7.6% to 9.0%, and 13.25 units (n=4464) for patients with pre-insulin HbA1c level > 9.0%. In patients with HbA1c level ≤ 9.0% altogether, the mean insulin daily dose at insulin initiation was 11.50 units (n=7265). The insulin daily dose increased during the study in all classes of pre-insulin HbA1c. The mean change in insulin daily dose observed between insulin initiation and final visit was +6.44 units (n=2516) for patients with HbA1c < 7.6%, +9.07 units (n=4749) for patients with HbA1c comprised between 7.6% and 9.0%, and +11.67 units (n=4464) for patients with pre-insulin HbA1c level > 9.0%. In patients with HbA1c level ≤ 9.0% altogether, the mean insulin daily dose increased by 8.16 units (n=7265).

- In patients who were prescribed DPP-IV inhibitors therapy prior to and at insulin initiation, the mean insulin daily dose was 13.52 units (n=594) at insulin initiation; it had increased by +10.60 units (n=594) at the final visit. In patients who discontinued DPP-IV inhibitors at insulin initiation, the mean insulin starting daily dose was 12.67 units (n=360); however it had increased by +20.33 units (SD: 26.84, n=360) at the final visit.

In terms of glycaemic control:

- The proportion of patients who reached the target HbA1c level of < 6.5% decreased with increasing BMI: it was 19.9% for patients with BMI < 25 kg/m² (n=2584), 14.5% for patients with BMI of 25-30 kg/m² (n=4724), 10.5% for patients with BMI of 30-35 kg/m² (n=2701), and 9.3% for patients with BMI ≥ 35 kg/m² (n=1529). Similarly, the proportion of patients who achieved a level of HbA1c < 7.0% ranged from 40.8% with BMI < 25 kg/m² down to 23.3% with BMI ≥ 35 kg/m².

- The proportion of patients who reached an HbA1c level < 6.5% or < 7.0% at the final visit was higher in patients with 1 OAD (< 6.5%: n=634/3317, 19.1%; < 7.0%: n=1355/3317, 40.9%) than in patients who received 2 OADs (< 6.5%: 776/6388, 12.1%; < 7.0%: n=1916/6388, 30.0%) or > 2 OADs (< 6.5%: 207/1881, 11.0%; < 7.0%: n=508/1881, 27.0%) prior to insulin initiation.

- The proportion of patients who had achieved an HbA1c level < 6.5% or < 7.0% at the final visit.
visit was 21.5% (n=280/1302) and 44.7% (n=582/1302) respectively for biguanides adherents. Achievement of these target HbA1c levels was less frequent among sulphonylurea adherents (< 6.5%: 15.1%, n=62/410; < 7.0%: 38.5%, n=158/410), and among biguanides plus sulphonylureas adherents (< 6.5%: 9.0%, n=221/2452; < 7.0%: 24.3%, n=597/2452).

- The proportion of patients achieving a level of HbA1c < 6.5% or < 7.0% at the final visit was 9.8% (n=44/449) and 37.2% (n=167/449) respectively for patients with DPP-IV inhibitors prior to and at insulin initiation. These proportions were 5.1% (n=14/277) and 24.5% (n=68/277) respectively in patients who discontinued DPP-IV inhibitors at insulin initiation.

Safety Results

Adverse drug reactions (FAS)

The number of patients with any SADR or major hypoglycaemic event was 27, that is, 0.2% of the FAS population. Eighteen patients presented 23 SADRs during the study follow-up and 154 patients (that is, 0.9% of the FAS patient population) presented 216 non-serious ADRs. Overall 21 patients experienced at least one major hypoglycaemic event between the baseline and final visits. It is to be noted that 8 patients in the UK and one patient in Portugal had major hypoglycaemias captured in the CRF but not notified as SADRs.

From the 216 non-serious ADRs, 142 (66.4%) were of mild severity, 58 (27.1%) of moderate severity, and 14 (6.5%) were severe; information was missing for 2 ADRs. The relationship to Levemir® was considered possible for 110 ADRs (51.6%), probable for 102 ADRs (47.9%), and not applicable for one ADR (0.5%); information was missing for 3 ADRs.

At the end of the follow-up period the outcome was “recovered” for 156 ADRs (72.9%), “recovering” for 23 ADRs (10.7%), “not recovered” for 27 ADRs (12.6%), and unknown for 8 ADRs (3.7%); this information was missing for 2 ADRs. Information on drug withdrawal was available for 215 of the 216 ADRs; drug withdrawal was required in 104 cases (48.4%). Dose change was applied in 98 of 114 ADRs where this information was provided.

The 216 ADRs pertained to 19 different SOCs. Out of the 154 patients with ADRs, 62 patients experienced 69 events pertaining to the General disorders and administration site conditions SOC and 43 patients experienced 53 events pertaining to the Skin and subcutaneous tissue disorders SOC. The most frequent events across all SOCs were the following: rash (Skin and subcutaneous tissue disorders; n=15 patients, n=15 events), injection site reaction (General disorders and administration site conditions; n=13 patients, n=13 events), pruritus (Skin and subcutaneous tissue disorders; n=10 patients, n=10 events), injection site haematoma (General disorders and administration site conditions; n=8 patients, n=8 events), hypoglycaemia (Metabolism and nutrition disorders; n=8 patients, n=8 events), and drug hypersensitivity (Immune system disorders; n=7 patients, n=7 events).

Eighteen patients presented 23 SADRs during the study follow-up. From these 23 SADRs, 3 were of mild severity, 4 of moderate severity, and 4 were severe; information was missing for 12 SADRs. The relationship to Levemir® as reported by the corresponding investigator was considered possible for 11 SADRs (47.8%), and probable for 12 SADRs (52.2%). As determined by the IPS, the relationship to Levemir® was considered possible for 18 SADRs (78.3%), and unlikely for 5 SADRs (21.7%).

At the end of the follow-up period the outcome was “recovered” for 22 of the 23 SADRs (95.7%), and fatal for one SADR (4.3%). The SADR that was fatal was a fall with craniocerebral injury.
Information on action taken was available for 19 out of the 23 SADRs. This information was as such: the product was withdrawn in 3 cases (3/19, 15.8%), the dose was reduced in 9 cases (9/19, 47.4%), there was no change regarding the study drug in 6 cases (6/19, 31.6%) and no action was reported in the last case (1/19, 5.3%).

From the 17 patients reporting any SADR, 12 experienced 14 SADRs pertaining to the Metabolism and nutrition disorders SOC; these SADRs were hypoglycaemia (n=9 patients, n=10 events), hypoglycaemia unawareness (n=1 patient, n=1 event), and hypoglycaemia unconsciousness (n=3 patients, n=3 events).

The other SADRs were atrial fibrillation (Cardiac disorders, n=1 patient, n=1 event), drug hypersensitivity (Immune system disorders, n=1 patient, n=1 event), urinary tract infection (Infection and Infestations, n=1 patient, n=1 event), fall (injury, poisoning and procedural complications, n=1 patient, n=1 event), blood glucose decreased (Investigations, n=1 patient, n=1 event), musculoskeletal pain (Musculoskeletal and connective tissue disorders, n=1 patient, n=1 event), cerebrovascular accident (nervous system disorder, n=1 patient, n=1 event), depression (Psychiatric disorders, n=1 patient, n=1 event) and treatment non-compliance (Social circumstances, n=1 patient, n=1 event).

During the 12 weeks prior to insulin initiation (4 weeks in the UK), 85 patients (n=85/17341, 0.5%) experienced any major hypoglycaemic event. Most events were diurnal. From these 85 patients, 75 (n=75/17336, 0.4%) reported a daytime event and 18 (n=18/17333, 0.1%) a nocturnal event. Thirteen patients (n=13/15880, 0.1%) reported any major hypoglycaemic event between baseline and the interim visit, and 15 patients (n=15/15003, 0.1%) between the interim and final visits. The proportion of patients with daytime events was < 0.1% (n=6/15877) at the interim visit and 0.1% (n=12/15000) at the final visit; the proportion of patients with nocturnal events was < 0.1% at both visits (n=5/15876 and n=1/15000, respectively).

In patients assessable for change, the rate of overall and daytime major events per patient-year decreased at the interim and final visits, compared to pre-insulin values. In patients with data at pre-insulin and interim assessments (a) and pre-insulin and final visit (b), the rate of major events prior to insulin initiation was 0.046 (a) and 0.043 (b) overall events per patient-year, respectively, 0.037 (a) and 0.039 (b) daytime events, respectively, and 0.006 nocturnal events. A reduction of overall major events from pre-insulin values was observed at the interim visit (mean change: -0.041 events per patient-year, n=15807, p < 0.001) and at the final visit (mean change: -0.038 events per patient-year, n=14760, p < 0.001). A significant reduction of daytime events was also observed at the interim visit (mean change: -0.037 events per patient-year, n=15806, p < 0.001) and at the final visit (mean change: -0.032 events per patient-year, n=14759, p < 0.001). The mean rate of nocturnal events was reduced by -0.004 (n=15801, p=0.001) and by -0.006 events per patient-year (n=14754, p < 0.001) at the interim and final visits, respectively.

The proportion of patients who experienced at least one minor hypoglycaemic event was 4.7% (n=812/17349) during the 4 weeks preceding insulin initiation, 6.6% (n=1056/15904) before the interim visit, and 6.2% (n=930/15030) in the 4 weeks preceding the final visit. Daytime events were reported by 3.4% (n=579/17167) of patients prior to insulin initiation, 5.5% (n=873/15815) at the interim visit and 5.2% (n=776/14960) at the final visit. Nocturnal minor hypoglycaemic events were less frequent, with 0.9% (n=146/17049) of patients experiencing them prior to insulin initiation, and 1.3% at the interim visit (n=209/15677) and at the final visit (n=187/14810).

The number of overall and daytime minor events per patient-year increased at the interim and final
visits, compared to pre-insulin values. In patients with data at pre-insulin and interim assessments (a) and pre-insulin and final visit (b), the rate of minor events prior to insulin initiation was 1.567 (a) and 1.577 (b) overall events per patient-year, respectively. 1.307 (a) and 1.314 (b) daytime events, respectively, and 0.268 (a) and 0.267 (b) nocturnal events, respectively. The mean change in the occurrence of overall minor events per patient-year was +0.402 (n=15700, p < 0.001) and +0.256 events per patient-year (n=14849, p < 0.001) at the interim and final visits, respectively. The mean change in rate of daytime minor events per patient-year was +0.336 (n=15641, p < 0.001) and +0.248 events per patient-year (n=14791, p < 0.001) at the interim and final visits, respectively. Finally, a significant increase in the rate of nocturnal minor events was also observed at the interim visit (mean change: +0.054 events per patient-year, n=15408, p=0.006), but not at the final visit.

Changes in weight and BMI, waist and hip circumferences (FAS)
Small but statistically significant reductions of weight, BMI, waist and hip circumferences were observed after the introduction of insulin.

In the 15672 patients assessable for change between pre-insulin and interim visit values, the mean weight decreased by -0.36 kg, from 80.98 kg prior to insulin initiation to 80.62 kg at the interim visit (p < 0.001). Similarly, the mean weight decreased by -0.56 kg from a pre-insulin value of 80.82 kg to a final visit value of 80.26 kg (n=14830, p < 0.001).

The mean BMI decreased by -0.12 kg/m$^2$, from 29.24 kg/m$^2$ prior to insulin initiation to 29.12 kg/m$^2$ at the interim visit (n=15445, p < 0.001), and by -0.17 kg/m$^2$ from a pre-insulin value of 29.19 kg/m$^2$ to a final visit value of 29.03 kg/m$^2$ (n= 14624, p < 0.001).

The mean waist circumference decreased by -0.41 cm, from 98.46 cm prior to insulin initiation to 97.33 cm at the interim visit (n=7034, p < 0.001). Similarly, the mean waist circumference decreased from a pre-insulin value of 98.29 cm to a final visit value of 97.60 cm, with a mean reduction of -0.69 cm (n=6666, p < 0.001). The mean hip circumference decreased by -0.44 cm, from 103.62 cm prior to insulin initiation to 103.18 cm at the interim visit (n=5157, p < 0.001), and by -0.66 cm from a pre-insulin value of 103.47 cm to a final visit value of 102.80 cm (n=4885, p < 0.001).

Systolic and diastolic blood pressure
Compared to pre-insulin values, there was a significant decrease in systolic and diastolic blood pressure from pre-insulin values at the interim visit (systolic: mean change: -3.39 mmHg, n=12093, p < 0.001; diastolic: mean change: -1.57 mmHg, n=12076, p < 0.001) and at the final visit (systolic: mean change: -4.10 mmHg, n=11459, p < 0.001; diastolic: mean change: -2.04 mmHg, n=11436, p < 0.001).

Subgroup analyses
Safety outcomes were similar across the different classes of Levemir® subgroups, with the exceptions detailed below.

In terms of ADRs, SADRs and hypoglycaemic events:
- The incidence of hypoglycaemic events, SADRs and ADRs was comparable among patients aged < 75 years or ≥ 75 years; the proportion of patients experiencing any hypoglycaemic events was 11.4% (n=1449/12732) and 10.3% (n=212/2058) respectively. Patients < 75 years of age tended to experience more minor events than patients aged ≥ 75 years prior to insulin
initiation (<75 years: 1.650 events per patient-year, n=12718; ≥75 years: 1.124 events per patient-year, n=2047) but not at the final visit (<75 years: 1.817 events per patient-year, 12718; ≥75 years: 1.969 events per patient-year, n=2047).

- The incidence of SADRs and ADRs was comparable in the four BMI classes. However, the proportion of patients reporting any hypoglycaemic events (major or minor) decreased with increasing BMI. The proportion of patients reporting any hypoglycaemic event (minor or major) during the study was 15.2% (n=466/3070) of patients with BMI < 25 kg/m², 11.2% (n=660/5881) of patients with BMI of 25-30 kg/m², 9.4% (n=339/3594) of patients with BMI of 30-35 kg/m², and 8.9% (n=181/2028) of patients with BMI ≥ 35 kg/m². The difference across BMI classes was observed with respect to minor hypoglycaemic events. The mean rate of overall minor hypoglycaemic events observed at the final visit was 2.390 events per patient-year, 2.009 events per patient-year, 1.471 events per patient-year, and 1.292 events per patient-year in patients with BMI < 25 kg/m², of 25-30 kg/m², of 30-35 kg/m², and ≥ 35 kg/m², respectively.

- The incidence of SADRs and ADRs was comparable in patients with 1 OAD, 2 OADs and >2OADs prior to insulin initiation; however the proportion of patients with any hypoglycaemic event (major or minor) tended to increase with the number of pre-insulin OADs. The proportion of patients reporting any hypoglycaemic event (minor or major) during the study was 8.5% (n=380/4446) of patients with 1 OAD, 11.8% (n=934/7904) for patients with 2 OADs, and 14.0% (n=321/2288) of patients with > 2 OADs, respectively. The difference across OAD classes was observed with respect to minor hypoglycaemic events. The mean rate of overall minor hypoglycaemic events observed at the final visit was 1.409 events per patient-year, 1.900 events per patient-year, and 2.158 events per patient-year in patients treated with 1 OAD, 2 OADs, or > 2 OADs prior to insulin initiation, respectively.

- The incidence of SADRs and ADRs was comparable in biguanides, sulphonylureas, and biguanides plus sulphonylureas adherents; however the proportion of patients with any hypoglycaemic event (major or minor) was lower in biguanides adherents than in the other two classes. The proportion of patients reporting any hypoglycaemic event (minor or major) during the study was 5.1% (n=92/1803) of biguanides adherents, 9.7% (n=53/547) of sulphonylureas adherents, and 9.9% (n=298/3003) of biguanides plus sulphonylureas adherents, respectively. The mean rate of overall minor hypoglycaemic events observed at the final visit was 0.826 events per patient-year, 1.529 events per patient-year, and 1.640 events per patient-year in biguanides, sulphonylureas, and biguanides plus sulphonylureas adherents, respectively.

- In patients with continued DPP-IV inhibitors therapy, the incidence of minor hypoglycaemic events increased during the study follow-up more than in patients who discontinued DPP-IV inhibitors therapy at insulin initiation. The mean number of overall minor hypoglycaemic events increased from 0.507 events per patient-year prior to insulin initiation to 3.261 events per patient-year at the final visit (change: +2.754, n=590, p=0.008) in patients with continued DPP-IV inhibitors therapy, and from 1.329 events per patient-year prior to insulin initiation to 1.616 events per patient-year at the final visit (change: +0.287, n=362, NS) in patients who discontinued DPP-IV inhibitors therapy at insulin initiation.

- Patients with pre-insulin hypoglycaemic events experienced more hypoglycaemic events during the study than patients without prior events. The incidence of any hypoglycaemic event (minor or major) was three times higher in patients with pre-insulin events (n=221/746,
29.6%) than in patients without pre-insulin events (n=1446/14104, 10.3%). Minor events were reported from baseline to the interim visit and from the interim visit to the final visit by 17.9% (n=109/608) and 15.4% (n=94/6102) of patients with pre-insulin hypoglycaemic events, compared to 5.8% (n=818/14031) and 5.5% (n=780/14228) of patients without pre-insulin hypoglycaemic events, respectively. The mean rate of minor events observed at the final visit was 4.461 overall events per patient-year (of which 1.088 nocturnal events) for patients with pre-insulin events, and 1.720 overall events per patient-year (of which 0.250 nocturnal events), in patients without pre-insulin events. A difference between these two classes was also observed for the rate of major events. The mean rate of major hypoglycaemic events (all by daytime) at the final visit was 0.041 events per patient-year in patients with and 0.003 events per patient-year in patients without pre-insulin events. Finally, it is to be noticed that the incidence of non-serious ADRs was higher in patients with pre-insulin events (n=14/849, 1.6%) than in patients without pre-insulin events (n=138/16489, 0.8%).

In terms of weight and BMI:

- Patients with initial BMI < 25 kg/m2 had gained weight at the final visit with a mean change of +0.75 kg (n=3079, p < 0.001) whereas a significant weight loss was observed for the other BMI classes compared to pre-insulin weight. The magnitude of the weight loss increased in line with the BMI, from 0.16 kg for patients with BMI of 25-30 kg/m2 to 1.89 kg for patients with BMI ≥ 35 kg/m2.

- Weight change at the final visit was on average -0.81 kg (n=4412, p < 0.001) in patients with pre-insulin therapy with 1 OAD, -0.47 kg for patients with 2 OADs (n=7890, p < 0.001), and -0.34 kg for patients with > 2 OADs prior to insulin initiation (n=2303, p=0.006).

- Biguanides adherents had a larger weight loss (mean change: -1.33 kg, n=1790, p < 0.001) than sulphonylureas (mean change: -0.48 kg, n=540, p=0.005) and biguanides and sulphonylureas adherents (mean change: -0.34 kg, n=2996, p < 0.001) at the final visit, compared to pre-insulin weight.

- Patients with pre-insulin hypoglycaemic events had a larger weight loss (mean change: -0.79 kg, SD: 3.96, n=730, p < 0.001) than patients without pre-insulin hypoglycaemic events (mean change: -0.55 kg, SD: 5.78, n=14075, p < 0.001) at the final visit, compared to pre-insulin weight.

In terms of blood pressure:

- Blood pressure tended to increase with the BMI. The mean systolic blood pressure was 130.97 mmHg (n=2535) in patients with BMI < 25 kg/m2, 135.16 mmHg (n=4535) in patients with BMI of 25-30 kg/m2, 138.77 mmHg (n=2693) in patients with BMI of 30-35 kg/m2, and 139.88 mmHg (n=1562) in patients with BMI ≥ 35 kg/m2. The mean diastolic blood pressure was 78.07 mmHg (n=2535) in patients with BMI < 25 kg/m2, 80.51 mmHg (n=4525) in patients with BMI of 25-30 kg/m2, 81.72 mmHg (n=2683) in patients with BMI of 30-35 kg/m2, and 82.20 mmHg (SD: 10.56, n=1559) in patients with BMI ≥ 35 kg/m2. The reduction in blood pressure observed during the study period was also higher with higher BMI. The mean systolic blood pressure had decreased at the final visit by -3.03 mmHg (n=2535, p < 0.001), -3.77 mmHg (n=4535, p < 0.001), -5.06 mmHg (n=2693, p < 0.001), and -5.10 mmHg (n=1562, p < 0.001) in the 4 BMI classes, respectively. The mean diastolic blood pressure had decreased at the final visit by -1.26 mmHg (n=2535, p < 0.001), -2.31 mmHg...
Conclusion:

Treatment with insulin detemir once-daily as add-on therapy over a period of 24 weeks in 17374 patients with type 2 diabetes uncontrolled by their OAD regimen recruited from 10 countries resulted in the following:

- Improvement of glycaemic control compared with the pre-insulin status, as shown by the reduction in HbA1c level over time (interim visit: -1.06%, n=9027, p < 0.001; final visit: -1.30%, n=9630, p < 0.001); reduction of FPG concentration over time (interim visit: -2.81 mmol/L, n=6252, p < 0.001; final visit: -3.06 mmol/L, n=6251, p < 0.001); decrease in FPG variability (interim visit: -1.04 mmol/L, n=3678, p < 0.001, final visit: -0.97 mmol/L, n=3638, p < 0.001). In patients with data, a reduction of the mean blood glucose was observed at all time points of the 7-point blood glucose profile between baseline and final visits.

- Improvement of the lipid profile from pre-insulin assessment to the final visit, with a significant reduction of total cholesterol level (-0.30 mmol/L, n=5962, p < 0.001), LDL-C (-0.16 mmol/L, n=4792, p < 0.001) and triglycerides level (-0.29 mmol/L, n=5649, p < 0.001)

- A low incidence of adverse drug reactions: the number of patients with any SADR or major hypoglycaemic event was 27, that is, 0.2% of the FAS population. Eighteen patients presented 23 SADRs during the study follow-up and 154 patients (that is, 0.9% of the FAS patient population) presented 216 non-serious ADRs.

- A low incidence of major hypoglycaemic events: the proportion of patients with daytime events was < 0.1% (n=6/15877) at the interim visit and 0.1% (n=12/15000) at the final visit; the proportion of patients with nocturnal events was < 0.1% at both visits (n=5/15876 and n=1/15000, respectively). In patients assessable for change, the rate of overall and daytime major events per patient-year decreased at the interim and final visits, compared to pre-insulin values.

- A slight increase in the incidence of minor hypoglycaemic events at final visit compared to the pre-insulin data. The proportion of patients experiencing any minor hypoglycaemia was 4.7% in the 4 weeks preceding insulin initiation (n=812/17349), 6.6% at the interim visit (n=1056/15904), and 6.2% at the final visit (n=930/15030). The mean change in the occurrence of overall minor events per patient-year was +0.402 (n=15700, p < 0.001) and +0.256 events per patient-year (n=14849, p < 0.001) at the interim and final visits, respectively. The mean change in rate of daytime minor events per patient-year was +0.336 (n=15641, p < 0.001) and +0.248 events per patient-year (n=14791, p < 0.001) at the interim and final visits, respectively. Finally, a significant increase in the rate of nocturnal minor events was also observed at the interim visit (mean change: +0.054 events per patient-year, n=15408, p=0.006), but not at the final visit, compared to the pre-insulin values.

- A significant decrease in mean weight and BMI between pre-insulin and final visit assessments (weight change: -0.56 kg, n=14830, p < 0.001; BMI change: -0.17 kg/m², n=14624, p < 0.001), as well as a reduction of waist and hip circumferences (waist change: -0.69 cm, n=6666, p < 0.001; hip change: -0.66 cm, n=4885, p < 0.001)

- A significant reduction in systolic and diastolic blood pressures between pre-insulin and final visit assessments (systolic: mean change: -4.10 mmHg, n=11459, p < 0.001; diastolic: mean...
change: -2.04 mmHg, n=11436, p < 0.001).

- A significant improvement in the patient’s appraisal of insulin administration (mean change in ITAS overall score: -3.52, n=6860, p < 0.001) and a reduction in patient’s depressive feelings (mean change: -2.35, n=800, p < 0.001) between the baseline and final visits.

This non-interventional study confirmed that insulin detemir administered once daily as add-on to OADs was a safe and effective option for patients with diabetes type 2 not effectively controlled by OAD therapy. No treatment restriction owing to patients’ characteristics has been identified.