2 Synopsis

Trial Registration ID-number NCT00474045	**EudraCT number –** 2006-004861-33
Title of Trial A randomised, parallel-group, open-labelled, multinational trial comparing the efficacy and safety of insulin detemir (Levemir®) versus human insulin (NPH insulin), used in combination with insulin aspart as bolus insulin, in the treatment of pregnant women with type 1 diabetes.	
Investigators A total of 79 principal investigators participated in the trial. Dr. [redacted] and Dr. [redacted] both from [redacted], [redacted] were appointed as signatory investigators for the trial.	
Trial Sites The trial was conducted at 79 trial sites in 17 countries.	
Publications None	
Trial Period 14 May 2007 to 5 August 2010	**Development Phase** Phase 3b

Objectives

Primary Objective:

To compare the glycaemic control measured as HbA_{1c} obtained by using either IDet or NPH at gestational week (GW)=36 (Visit P4)

Secondary Objectives:

Efficacy Objectives

To compare the two treatments with respect to:

- HbA_{1c} during the pregnancy period
- Number of subjects with $HbA_{1c} \leq 6.0\%$ both at GW=24 (Visit P3) and GW=36 (Visit P4)
- 8-point self-measured plasma glucose (SMPG) profiles during the pregnancy period
- Fasting plasma glucose (FPG) values during the pregnancy period

Safety Objectives (Maternal)

To compare the two treatments with respect to:

- Incidence of hypoglycaemic episodes (symptoms only + minor and major episodes) for 24h period and nocturnal during the pregnancy period
- Mode of delivery (vaginal and caesarean section)
- Safety profiles including adverse event (AE) data and laboratory parameters during the pregnancy period
- Development of insulin antibodies during the trial (IDet, IAsp specific and cross-reacting antibodies)
- Deterioration of diabetes complications (nephropathy and retinopathy)

Safety Objectives (Pregnancy Outcome)

To compare the pregnancy outcome between the two treatments measured by:

- An abnormal pregnancy outcome defined by occurrence of at least one of the following:
  - Live born infants with birth weight < 10^{th} percentile for gestational age and sex (local reference)
  - Live born infants with birth weight > 90^{th} percentile for gestational age and sex (local reference)
  - Pre-term delivery (delivery < 37 completed GWs)
  - Early foetal death (< 22 completed GWs)
  - Perinatal mortality (death of a foetus/infant between ≥ 22 completed GWs and < 1 completed week after delivery)
  - Neonatal mortality (post partum death [pp] after 7 completed days and before 28 completed days after delivery)

– Presence of major malformations
- Presence of insulin antibodies (IDet specific, IAsp specific and cross-reacting antibodies) in cord blood
- Presence of IDet in cord blood
- AEs

Methodology

This trial was a randomised (1:1), open-labelled, multinational, parallel group trial comparing the safety and efficacy of IDet versus NPH, both used in combination with IAsp in a basal-bolus regimen in the treatment of pregnant women with type 1 diabetes.

Subjects who provided consent to participate were randomised to either IDet or NPH as basal treatment. Both groups used IAsp as meal time insulin and the subjects were followed throughout their pregnancy, with one trial visit scheduled for each trimester.

Subjects were enrolled (and randomised to treatment) either non-pregnant or pregnant from 8 up until 12 completed GWs (confirmed by ultra sound scan). Subjects who were randomised non-pregnant attended the non-pregnant visits according to standard practice for each centre. Trial visits were to take place at three-monthly intervals with phone contacts every 2-12 weeks until conception was confirmed or the subject was withdrawn. Thus, the trial duration and number of visits could vary depending on the time of conception relative to the point of enrolment. The maximum duration was 23 months (with delivery at 40 weeks).

Subjects were not allowed to remain non-pregnant in the trial for more than 12 months from time of randomisation; subjects who did not conceive within 12 months from randomisation were withdrawn from the trial. Additionally, non-pregnant subjects who did not reach an $HbA_{1c} \leq 8.0\%$ after 9 months post randomisation (Visit 5) were also withdrawn from the trial.

During the pregnancy period, trial visits were scheduled to obtain data from each trimester and since a large proportion of diabetic women usually deliver some weeks before full term, and in order not to rely on data collection in the hectic setting of ongoing labour, the visits were spaced evenly backwards from GW = 36 weeks, at which point only a minority of the women were expected to have delivered.

A follow-up (FU) visit was planned to take place 6 weeks after delivery after which the subjects were to be offered to continue treatment with commercially available insulin at the discretion of the investigator.

Number of Subjects Planned and Analysed

It was planned to randomise 460 subjects to obtain 240 completers. A total of 600 subjects were screened, 130 of which were screening failures. The numbers of subjects included in the trial are shown below.

	Detemir N (%)	NPH N (%)	Total N (%)
Screened			600
Screening Failures			130
Randomised	233 (100.0)	237 (100.0)	470 (100.0)
Exposed	233 (100.0)	232 (97.9)	465 (98.9)
Randomised and Pregnant Subjects			
Randomised	152 (100.0)	161 (100.0)	313 (100.0)
Exposed	152 (100.0)	158 (98.1)	310 (99.0)
Withdrawals	25 (16.4)	25 (15.5)	50 (16.0)
Completed Trial	127 (83.6)	136 (84.5)	263 (84.0)

Diagnosis and Main Criteria for Inclusion

Women, aged ≥ 18 years, with type 1 diabetes treated with insulin (any regimen) for at least 12 months before randomisation; the subject was either planning to become pregnant in the immediate future and willing to undertake pregnancy counselling and a screening $HbA_{1c} \leq 9.0\%$ (National Glycohaemoglobin Standardization Program [NGSP]) *or* was pregnant with an intrauterine singleton living foetus, GW: 8-12 at randomisation, confirmed by an ultrasound scan and an $HbA_{1c} \leq 8.0\%$ at confirmation of pregnancy were included in the trial.

Test Product, Dose and Mode of Administration, Batch Number

IDet, 100 U/mL, 3 mL cartridge was administered using NovoPen®3 Forest Green pen. IDet was administered subcutaneously at the same time as the basal insulin was given prior to randomisation and the dose adjusted according to the titration guideline. Subjects were instructed to rotate the site of injection within the area chosen in order to prevent lipo-hypertrophy. The insulin dose was to be taken at approximately the same time each day. For Batch Numbers see the Table below.

Trial Product	Concentration	Batch Number	Expiry Date
IDet, 100 U/mL, 3 mL cartridge	100 U/mL	Q50422	09 June 2009 14 October 2010 22 December 2011

Duration of Treatment

The trial duration and number of visits for each subject varied depending on the time of conception relative to the point of enrolment. The maximum period was 23 months (with delivery at 40 weeks).

Reference Therapy, Dose and Mode of Administration, Batch Number

NPH, 100 IU/mL, 3 mL cartridge was administered using NovoPen®3 Forest Green pen. NPH was administered similarly to IDet. For Batch Numbers see the Table below.

Trial Product	Concentration	Batch Number	Expiry Date
NPH, 100 IU/mL, 3 mL cartridge	100 IU/mL	SQ50876 TFF0035 VQ50194	27 May 2009 02 October 2009 29 November 2011

IAsp, 100 U/mL, 3 mL cartridge was administered using NovoPen®3 Silver. IAsp was used as bolus insulin. IAsp was administered subcutaneously. IAsp was used in connection with main meals. Doses were adjusted according to the size of the meal. For Batch Numbers see the Table below.

Trial Product	Concentration	Batch Number	Expiry Date
IAsp, 100 U/mL, 3 mL cartridge	100 U/mL	SQ50686 VU50005 VQ50208	13 September 2008 07 July 2010 14 October 2010

Criteria for Evaluation – Efficacy

- HbA_{1c}
- 8-point SMPG profiles
- FPG

Criteria for Evaluation – Safety

- Maternal Safety
  - Hypoglycaemic episodes
  - Mode of delivery
  - AEs
  - Retinopathy and nephropathy
  - Clinical Laboratory Tests

- Vital signs and weight
- ECG
- Insulin antibodies
- Insulin doses

- Pregnancy Outcome and Safety in Children
  - Pregnancy Outcome/Neonatal Assessments
  - AEs in children
  - General assessments and conditions at birth and follow up
  - Insulin antibodies and IDet in cord blood

Statistical Methods

The Full Analysis Set for pregnant subjects ($FAS_{Pregnant}$) was used for analyses of all efficacy endpoints and comprised all randomised subjects who were exposed to at least one dose of trial product and who were pregnant during the trial. Subjects were classified according to randomised treatment.

The Per Protocol Analysis Set for pregnant subjects ($PP_{Pregnant}$) was used for the analysis of the primary endpoint (HbA_{1c} at GW 36), and two secondary efficacy endpoints (HbA_{1c} at GW 24 and HbA_{1c} at delivery). $PP_{Pregnant}$ comprised all subjects from the $FAS_{Pregnant}$ analysis set for whom gestational age at delivery was at least 32 completed weeks and with no other protocol violations with influence on the primary endpoint. The analysis based on the $FAS_{Pregnant}$ analysis set and the analysis based on $PP_{Pregnant}$ analysis set were of equal importance for the test of non-inferiority, and non-inferiority was only declared if the non-inferiority criterion was fulfilled for both $FAS_{Pregnant}$ and $PP_{Pregnant}$. The $PP_{Pregnant}$ analysis was supportive for the test of superiority.

The Safety Analysis Set for pregnant subjects ($Safety_{Pregnant}$) comprised all randomised subjects who were exposed to at least one dose of trial product and who were pregnant during the trial. Safety was evaluated using the $Safety_{Pregnant}$ analysis set. Pregnancy outcome was evaluated using the $Safety_{Pregnant}$ analysis set. Subjects were classified according to actual treatment.

Non-inferiority and superiority were formulated and tested as a one-sided hypothesis at a 2.5% level of significance.

Primary Efficacy Endpoint

The primary endpoint was HbA_{1c} at GW = 36 (Visit P4). The primary endpoint was evaluated using a non-inferiority criterion. A one-sided test with a significance level of 2.5% and a 95% confidence interval [CI_{lower}; CI_{upper}] for the estimated treatment difference, IDet – NPH, was applied. A normal linear regression model was used to model the primary endpoint (using LOCF) with treatment, country and pregnancy status at randomisation as factors and HbA_{1c} at randomisation and the HbA_{1c} at randomisation by pregnancy status at randomisation interaction as covariates. Non-inferiority of IDet compared to NPH was declared if CI_{upper} was below the pre-specified non-inferiority margin of 0.4% for both $FAS_{Pregnant}$ and $PP_{Pregnant}$. If non-inferiority was established, it could subsequently be concluded that IDet was superior to NPH as measured by HbA_{1c} if CI_{upper} was less than zero. The $PP_{Pregnant}$ analysis was supportive for the test of superiority.

For $PP_{Pregnant}$, missing Visit P4 values were imputed using the value at the delivery visit, subsequently the value at Visit P3.

Secondary Efficacy Endpoints

The primary analysis with test for non-inferiority and superiority (if non-inferiority was shown) was repeated for HbA_{1c} at delivery for $FAS_{Pregnant}$ and for $PP_{Pregnant}$ (post-hoc). LOCF was made using visit P4 data only. The primary analysis was also repeated for HbA_{1c} at Visit P3 for $FAS_{Pregnant}$ (LOCF, post-hoc) and $PP_{Pregnant}$ (no LOCF, post-hoc).

Statistical analysis was made using the $FAS_{Pregnant}$ analysis set for the following endpoints the proportion of subjects reaching reaching $HbA_{1c} \leq 6.0\%$ both at Visit P3 and Visit P4, FPG at Visit P3 and Visit P4 and 8-point SMPG at Visit P3 and Visit P4.

The proportion of subjects reaching $HbA_{1c} \leq 6.0\%$ both at Visit P3 and Visit P4 (using LOCF) was analysed using a

logistic regression model with adjustment by treatment, pregnancy status at randomisation, HbA_{1c} at randomisation and the HbA_{1c} at randomisation by pregnancy status at randomisation interaction. The odds ratio and the 95 % CI for the odds ratio for treatment (IDet versus NPH) were calculated together with the p-value for test of no treatment effect.

FPG at Visit P3 (using LOCF) was analysed by a normal linear regression model including treatment, country and pregnancy status at randomisation as factors and FPG at randomisation and the FPG at randomisation by pregnancy status at randomisation as covariates. FPG at Visit P4 (using LOCF) was analysed using the same model. Based on the normal linear regression model, the estimated treatment differences for IDet versus NPH at each of the two visits were presented with the 95% CI. The p-value for test of no treatment effect was also presented.

The 8-point SMPG profiles measured at Visit P3 and Visit P4 were tested for parallelism (between IDet and NPH) using a linear mixed model, where time point (that is, time of measurement during the day) was the repeated measurement within a subject. The 8-point SMPG profiles were analysed at Visit P3 and Visit P4 separately. The fixed factors in the model were treatment, time point, country, time point by treatment interaction and pregnancy status at randomisation. An unstructured covariance structure (Visit P3) and a compound symmetry covariance structure (Visit P4) was applied for each subject. The observations were assumed completely independent between subjects. LOCF was applied. If the interaction between time point and treatment was statistically significant, the 8-point SMPG profiles cannot be regarded as parallel. In case of non-parallel profiles, the difference between treatments was estimated at each time point using the above model. If the interaction between time point and treatment was not statistically significant, the model was reduced by omitting the interaction and a common treatment effect for all time points were estimated based on the reduced model. The corresponding 95% CI and p-values were also presented.

Maternal Safety Endpoints

The difference between treatments was evaluated using descriptive statistics for the maternal safety endpoints. Formal statistical analyses were only performed for hypoglycaemic episodes during pregnancy for $Safety_{Pregnant}$.

The treatment emergent hypoglycaemic episodes during pregnancy were analysed with a negative binomial regression, where the number of episodes depends on treatment, pregnancy status at randomisation and country and where the log-transformed exposure time during pregnancy was seen as an offset variable. The estimated rate ratio between IDet and NPH together with the 95% CI and the corresponding p-value were presented.

The analysis was performed on all maternal treatment emergent hypoglycaemic episodes for the 24h data and the nocturnal (midnight-06:00) episodes during pregnancy. Similar analyses was performed for symptoms only, minor and major maternal treatment emergent hypoglycaemic episodes for the 24h data during pregnancy and symptoms only, minor and major nocturnal maternal treatment emergent hypoglycaemic episodes during pregnancy.

Furthermore, a sensitivity analysis of hypoglycaemic episodes was performed. For each class of hypoglycaemic episodes a separate sensitivity analysis was conducted comparing number of episodes pair-wise in the two treatment groups using the Wilcoxon-Mann-Whitney method.

Pregnancy Outcome Safety Endpoints

The difference between treatments for the pregnancy outcome endpoints was evaluated using descriptive statistics. Formal statistical analyses were only performed for the composite pregnancy outcome endpoint and for insulin antibodies.

The composite pregnancy outcome endpoint was analysed using logistic regression with treatment, pregnancy status at randomisation as factors. The odds ratio and the 95 % CI for the odds ratio for treatment (IDet versus NPH) were calculated together with the p-value for test of no treatment effect.

Insulin antibodies in cord blood from live-born infants were compared with the amount of maternal insulin antibodies. This was done by comparing the ratio between the levels of maternal insulin antibodies at P4 with the levels of insulin antibodies in the cord blood. The ratio was analysed using a normal linear regression model with

treatment, country and pregnancy status at randomisation as factors. Based on the normal linear regression model, the estimated treatment differences for IDet versus NPH was presented with the 95% CI and the p-value for test of treatment effect.

Demography of Trial Population

The $Safety_{Pregnant}$ analysis set comprised 310 female subjects with type 1 diabetes, aged between 20 and 43 years. The majority of subjects (89%) were White. Mean BMI was slightly higher in the NPH group than in the IDet group, 25.2 vs 24.3 kg/m2. Approximately 52% of the subjects were pregnant at randomisation. Mean duration of diabetes was approximately 12 years (one year longer in the IDet group than in the NPH group). Mean HbA_{1c} was approximately 7.0% in both treatment groups and mean FPG was approximately 5.9 mmol/L in both treatment groups.

Efficacy Results

- **Primary Endpoint, HbA_{1c}:** Non-inferiority of IDet to NPH measured by HbA_{1c} at GW 36 was shown. The upper limit of the 95% CI for the estimated mean treatment difference in HbA_{1c} was below the prespecified non-inferiority criterion of 0.4% for both the
  $FAS_{Pregnant}$ analysis set (IDet-NPH [95% CI]; -0.06 [-0.21 ; 0.08]) and the
  $PP_{Pregnant}$ analysis set (IDet-NPH [95% CI]; -0.15 [-0.34 ; 0.04]).
  IDet was not superior to NPH.
  Estimated HbA_{1c} values at GW 36:
  $FAS_{Pregnant}$ analysis set, IDet 6.27%, NPH 6.33%
  $PP_{Pregnant}$ analysis set, IDet 6.22%, NPH 6.37%
- **Secondary Efficacy Endpoints**
  - **HbA_{1c} During the Pregnancy Period:** The development in mean HbA_{1c} through pregnancy was similar for subjects in the IDet and NPH groups. Mean HbA_{1c} decreased during the first two trimesters, and then increased from GW 24 to GW 36. Mean HbA_{1c} continued increasing post-pregnancy to reach a slightly lower level 6 weeks after delivery than measured at GW 10 (Visit P1).
  - **Subjects Reaching $HbA_{1c} \leq 6.0\%$ Both at P3 and P4:** The target of HbA1c ≤ 6.0% was reached by 41% of the subjects in the IDet group and by 32% in the NPH group. This difference was not statistically significant. The difference was more pronounced for subjects who became pregnant after randomisation (IDet 57%, NPH 41%) than for subjects who were pregnant at randomisation (IDet 37%, NPH 35%).
  - **FPG During the Pregnancy Period:** Mean FPG was statistically significantly lower for subjects in the IDet group than for subjects in the NPH group at both GW 24 and GW 36. The estimated mean difference (IDet-NPH [95% CI]) was -0.94 mmol/L [-1.67 ; -0.21] at GW 24 and
    -0.65 mmol/L [-1.19 ; -0.12] at GW 36.
    Estimated FPG values at GW 24: $FAS_{Pregnant}$ analysis set, IDet 5.38 mmol/L, NPH 6.32 mmol/L
    Estimated FPG values at GW 36: $FAS_{Pregnant}$ analysis set, IDet 4.76 mmol/L, NPH 5.41 mmol/L
  - **8-point SMPG During the Pregnancy Period:** The PG profiles at both GW 24 (Visit P3) and GW 36 (Visit P4) were parallel. At both visits mean PG appeared lower for subjects in the IDet group than for subjects in the NPH group. The difference was statistically significant at GW 24 but not at GW 36.
    The estimated mean difference (IDet-NPH [95% CI]) was -0.43 mmol/L [-0.72 ; -0.14] at GW 24 and -0.24 mmol/L [-0.51 ; 0.03] at GW 36.

Safety Results

Maternal Safety Endpoints During Pregnancy

- **Hypoglycaemic episodes:** There were no clinically relevant or statistically significant difference between treatment groups in “All episodes”, “Major episodes”, “Minor episodes” and “Symptoms Only” for episodes collected over 24 hours and for nocturnal episodes.
- **Mode of delivery:** There were no noteworthy differences between the two treatment groups in mode of delivery.
- **Maternal adverse events:** There was no clinically relevant difference between the two treatment groups in the reporting of AEs. The proportion of mothers having AEs during pregnancy was approximately 90% in both treatment groups. The rate of AEs was similar in both groups, a little less than 800 events per 100 exposure years.

Severe AEs occurred in a higher proportion of mothers (25% vs. 20%) and with a higher rate (77 vs. 51 events per 100 exposure years) in the IDet group than in the NPH group. The rate of adverse events considered possibly or probably related to investigational product was similar in the two treatment groups. The most frequently reported adverse events in both treatment groups were nasopharyngitis and headache. There were no injection site disorders in the NPH group and only 6 injection site reactions events in 6 mothers in the IDet group.

- **Maternal deaths, serious adverse events and other significant adverse events:** No women died during the trial. Three deaths in children were recorded – they are described under AEs in children. During pregnancy 61 (40%) mothers reported 94 serious adverse events in the IDet group while 49 (31%) subjects reported 76 serious adverse events in the NPH group. The event rate of SAEs was higher with IDet than with NPH (114 vs. 88 SAEs per 100 exposure years). The most frequent SAEs in the IDet group were related to spontaneous abortions, pre-eclampsia and hyperglycaemic conditions. In the NPH group the most frequent SAEs were related to spontaneous abortions and hypoglycaemic conditions. A higher percentage of subjects in the IDet group (8.6%) than in the NPH group (3.8%) withdrew from the trial during pregnancy due to AEs. The most frequent AEs leading to withdrawal in both treatment groups were related to spontaneous abortions.
- **Acceleration of Retinopathy and Nephropathy:** There were few cases and no difference between the two treatment groups in the proportion of subjects with acceleration of retinopathy or nephropathy.
- **Standard Laboratory Safety:** No clinically relevant differences between the treatment groups were observed in Haematology, Biochemistry or Urinalysis parameters.
- **Vital Signs:** There were no clinically relevant changes or differences between the treatment groups in pulse or blood pressure.
- **ECG:** No clinically significant changes or differences in ECGs between the treatment groups were observed.
- **Maternal Insulin Antibodies:** Levels of IDet specific, IAsp specific and cross reacting antibodies were in general low and there was no indication of a general increase during treatment.
- **Weight during Pregnancy:** There was no clinically significant difference between the treatment groups in weight gain during pregnancy (11.5 kg in the IDet group and 11.0 kg in the NPH group).
- **Insulin Dose during Pregnancy:** Doses of both basal and bolus insulin increased during pregnancy and decreased during follow up. The increase during pregnancy was most pronounced for bolus insulin. Mean doses of basal insulin were similar in the two treatment groups.

Pregnancy Outcome and Safety in Children

- **Pregnancy Outcome:** There were 128 live births (90%) in the IDet group and 136 live births (94%) in the NPH group. There were 11 early foetal deaths in the IDet group and 9 in the NPH group. These were mainly spontaneous abortions; 10 in the IDet group and 8 in the NPH group. In addition there were 1 ectopic pregnancy in each treatment group and 2 stillbirths in the IDet group. One perinatal death was recorded in the NPH group.
- **Composite Pregnancy Outcome:**
  The composite pregnancy outcome for outcomes within the trial period comprised:
  - Live-born infants with birth weight < 10^{th} percentile
  - Live-born infants with birth weight > 90^{th} percentile
  - Preterm delivery (delivery < 37 completed GWs)
  - Early foetal death (< 22 completed GWs)
  - Perinatal mortality
  - Neonatal mortality
  - Presence of major malformations

  There was no statistically, significant difference between the treatment groups for the composite pregnancy endpoint. Overall, there were 89 (63%) composite pregnancy events in the IDet treatment group and 96 (66%) events in the NPH treatment group.
- **Adverse Events in Children:** There was no clinically relevant difference between the treatment groups in the incidence of children having AEs (approximately 35% in both groups) or in the number of AEs per child (IDet 2.2 AEs per child, NPH 2.8 AEs per child). There was no difference between the treatment groups in the

incidence of children having severe AEs (IDet 10%, NPH 8%). The most frequent AEs were foetal distress syndrome, jaundice neonatal (or just jaundice) and premature baby. There were no noteworthy differences in incidence between the treatment groups for any of these events.

- **Deaths, serious adverse events and other significant adverse events in children:**
  - Three deaths in children were recorded. They were all three perinatal (2 in the IDet group and 1 in the NPH group).
  - A fairly similar proportion of the children in the two treatment groups had SAEs (24% in the IDet group and 20% in the NPH group). In the IDet group 1 SAE in a child (foetal distress syndrome) was by the investigator considered possibly related to treatments and none in the NPH group were. One SAE in a child in the NPH group ([redacted]) and none in the IDet group lead to withdrawal of the mother.
  - A total of 17 children (incidence of 5.5%) had congenital malformations (8 children in the IDet and 9 in the NPH group). Seven children had major and 10 had minor malformations. Major malformations occurred in 5 children in the IDet group and in 2 children in the NPH group. However, 4 mothers of children with major malformations had NPH during organogenesis and 3 mothers had IDet.
    All major malformations were by the investigators considered unlikely related to the trial treatment.
- **General assessments and conditions at birth, including neonatal hypoglycaemia:**
  - There were no noteworthy differences between the treatment groups in gestational age at delivery, birth weight or length, or Apgar score after 1 and 5 minutes
  - There were more children with neonatal hypoglycaemia in the NPH group than in the IDet group during the first 24 hours pp (24 vs. 15 children) but not during the period from 24–48 hours pp (6 vs. 4 children).
  - There were more children in the IDet group than in the NPH group with chest X-Ray consistent with respiratory distress syndrome (9 vs. 4 children) and more children in the IDet group needed treatment with nasal continuous positive airway pressure (11 vs. 3 children).
- **Insulin Antibodies in Cord Blood:** In general antibody levels were low, and mean, median and ranges were at approximately the same level as in the mothers.
- **Cord Blood IDet Levels:**
  IDet was below measuring range (<25.00 pmol/L) for 72 of 98 subjects. For the remaining 26 subjects with measurable IDet in the cord blood the maximum IDet concentration in cord blood was 209.6 pmol/L, which is approximately 20 times lower than C_{max} in subjects with type 1 diabetes following a single dose of 0.4 U/kg IDet.

Conclusions

In 310 pregnant women with type 1 diabetes exposed to a basal / bolus insulin regimen with IDet or NPH as basal insulin and IAsp as mealtime insulin the following conclusions were drawn:

- **Glycaemic control during pregnancy:**
  - IDet was non-inferior to NPH measured by HbA_{1c} at gestational week 36.
  - There was a clinically relevant and statistically significant difference in FPG in favour of IDet at both gestational week 24 and 36.
  - Mean PG was statistically significantly lower in the IDet group than in the NPH group at gestational week 24 (but not 36) based on 8-point self measured plasma glucose profiles.
  - A total of 41% of the subjects in the IDet group and 32% in the NPH group reached the target of $HbA_{1c} \leq 6.0\%$ at gestational week 24 and 36. This difference was not statistically significant.
  - In both treatment groups mean HbA_{1c} decreased during the first two trimesters, and then increased from week 24 to 36 and during post-pregnancy to reach a slightly lower level 6 weeks after delivery than at gestational week 10.
- **Maternal safety during pregnancy**
  - There was no clinically relevant or statistically significant difference between treatment groups in risk of having hypoglycaemic episodes.
  - There were no noteworthy differences between the two treatment groups in mode of delivery.

- There was no clinically relevant difference between the two treatment groups in the adverse event profile for the mothers.
- There were few cases and no difference between the two treatment groups in the proportion of subjects with acceleration of retinopathy or nephropathy.
- No clinically relevant differences between the treatment groups were observed in standard laboratory safety parameters, vital signs, ECG, or weight.
- Levels of IDet specific, IAsp specific and cross reacting antibodies in the mothers were in general low and there was no indication of a general increase during treatment or any difference between the treatment groups.
- Doses of both basal and bolus insulin increased during pregnancy and decreased during follow up. Mean doses of basal insulin were similar in the two treatment groups.

- **Pregnancy outcome and safety in children**
  - There were no clinically relevant differences between the treatment groups in number of live births, early foetal deaths or perinatal deaths. There were no neonatal deaths (between 7 and 28 days pp) or deaths during follow up (until 6 weeks pp).
  - There was no statistically, significant difference between the treatment groups for the composite pregnancy endpoint, comprising: Live-born infants with birth weight < 10^{th} percentile, Live-born infants with birth weight > 90^{th} percentile, Preterm delivery (delivery < 37 completed GWs), Early foetal death (< 22 completed GWs), Perinatal mortality, Neonatal mortality, Presence of major malformations.
  - There was no clinically relevant difference between the treatment groups in the adverse event profile for the children.
  - There were no noteworthy differences between the treatment groups in gestational age at delivery, birth weight or length, or Apgar score after 1 and 5 minutes.
  - There were more children with neonatal hypoglycaemia in the NPH group than in the IDet group during the first 24 hours pp (24 vs. 15 children) but not during the period from 24–48 hours pp (6 vs. 4 children).
  - There were more children in the IDet group than in the NPH group with chest X-Ray consistent with respiratory distress syndrome (9 vs. 4 children) and more children in the IDet group needed treatment with nasal continuous positive airway pressure (11 vs. 3 children).
  - In general antibody levels in cord blood were low, and mean, median and ranges were at approximately the same level as in the mothers.
  - The concentration of IDet in cord blood was below the lower level of quantification (<25.00 pmol/L) for 72 of 98 subjects. For the remaining 26 subjects with measurable IDet in the cord blood the maximum IDet concentration in cord blood was 209.6 pmol/L, which is approximately 20 times lower than C_{max} in subjects with type 1 diabetes following a single dose of 0.4 U/kg IDet.

In summary, in this population of pregnant women with type 1 diabetes, IDet was noninferior to NPH when used in combination with IAsp. No safety issues were identified from the results of this trial.

The trial was conducted in accordance with the Declaration of Helsinki (Washington 2004 edition) and ICH Good Clinical Practice.

The results presented reflect data available in the clinical database as of 20-Jan-2011.