Efficacy and safety of insulin detemir versus Neutral Protamine Hagedorn (NPH) insulin in pregnant women with type 1 diabetes

This trial is conducted in Africa, Europe, North and South America and Oceania.
The aim of this trial is to compare the effect and safety on blood glucose control in pregnant women with type 1 diabetes of a modern insulin analogue (insulin detemir) and human insulin (NPH insulin) given as long-acting insulin in combination with a short-acting insulin (insulin aspart).

Scientific Title
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

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<td>Diabetes Mellitus, Type 1</td>
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<td>Phase 3</td>
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<th>Treatment</th>
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<tbody>
<tr>
<td>• insulin detemir</td>
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<tr>
<td>• insulin NPH</td>
</tr>
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<td>• insulin aspart</td>
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<table>
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<th>Arm Information with Assigned Treatment</th>
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<tr>
<td>No. of arms: 2</td>
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<td>• Insulin detemir (Experimental):</td>
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<td>Arm description: Individually adjusted insulin detemir injected subcutaneously as basal insulin + individually adjusted insulin aspart injected subcutaneously as bolus insulin from randomisation (gestational week 8-12) and continued until 6 weeks after delivery. If a subject was not pregnant at randomisation, treatment was given up to a maximum of 52 weeks. For subjects who became pregnant, randomised treatment was continued until 6 weeks after delivery. Subjects who were not pregnant at 52 weeks after randomisation were</td>
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withdrawn
Drug: insulin detemir
Treat-to-target, dose titration, s.c. (under the skin) injection
Drug: insulin aspart
Treat-to-target, dose titration, s.c. (under the skin) injection

Neutral Protamine Hagedorn (NPH) insulin (Active Comparator):
Arm description: Individually adjusted NPH insulin injected subcutaneously as basal insulin + individually adjusted insulin aspart injected subcutaneously as bolus insulin from randomisation (gestational week 8-12) and continued until 6 weeks after delivery. If a subject was not pregnant at randomisation, treatment was given up to a maximum of 52 weeks. For subjects who became pregnant, randomised treatment was continued until 6 weeks after delivery. Subjects who were not pregnant at 52 weeks after randomisation were withdrawn
Drug: insulin NPH
Treat-to-target, dose titration, s.c. (under the skin) injection
Drug: insulin aspart
Treat-to-target, dose titration, s.c. (under the skin) injection

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<th>Trial status</th>
<th>No. of trial participants</th>
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<td>Completed</td>
<td>470</td>
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<th>Age eligible for trial participation</th>
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<tr>
<td>18 years and above</td>
<td>Female</td>
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Inclusion criteria
- Type 1 diabetes treated with insulin for at least 12 months
- Planning to become pregnant and have a screening HbA1c (glycosylated haemoglobin) lesser than or equal to 9.0%, or
- Pregnant with an intrauterine singleton living foetus, 8-12 weeks pregnant when joining the trial and a HbA1c lesser than or equal to 8.0% when pregnancy is confirmed

Exclusion criteria
- Known or suspected hypersensitivity to the trial product(s) or related products
- Untreated hyperthyroidism or hypothyroidism
- Known or suspected abuse of alcohol or narcotics
- Cardiac problems
- Impaired kidney function
- History of severe hyperemesis gravidarum
- Treatment with in-vitro fertilisation or other medical infertility treatment
- Impaired liver function
- Uncontrolled hypertension
- Proliferative retinopathy or maculopathy requiring acute treatment
- Known to be HIV (human immunodeficiency virus) positive, Hepatitis B or Hepatitis C positive
- Any concomitant medication contraindicated

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<table>
<thead>
<tr>
<th>Trial type</th>
<th>Trial design</th>
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<td>Interventional</td>
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<td>Allocation: Randomized</td>
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<td>Masking:</td>
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<td>Control: Active Control</td>
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<td>Assignment: Parallel Assignment</td>
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### Primary outcome
- Glycosylated Haemoglobin (HbA1c) for Full Analysis Set (Pregnant Subjects) at GW 36
  Time frame: At gestational week (GW) 36
- Glycosylated Haemoglobin (HbA1c) for Per Protocol Analysis Set (Pregnant Subjects) at GW 36
  Time frame: At gestational week (GW) 36

### Secondary outcome(s)
- Glycosylated Haemoglobin (HbA1c) During Pregnancy
  Time frame: During the pregnancy period
  [Visit P1 (GW 8-12), Visit P2 (GW 14), Visit P3 (GW 24), Visit P4 (GW 36), Delivery Visit (end of pregnancy)] and Follow-Up Visit (6 weeks after delivery)
- Subjects Reaching HbA1c at or below 6.0%
  Time frame: At both Visit P3 (GW 24) and Visit P4 (GW 36)
- Fasting Plasma Glucose (FPG)
  Time frame: During the pregnancy period
  [Visit P1 (GW 8-12), Visit P2 (GW 14), Visit P3 (GW 24), Visit P4 (GW 36)]
- 8-point self-monitored plasma glucose (SMPG) profile at GW 24
  Time frame: Visit P3 (GW 24)
- 8-point self monitored plasma glucose (SMPG) profile at GW 36
  Time frame: Visit P4 (GW 36)
- Maternal Safety - Number of Subjects with Adverse Events (AEs)
  Time frame: Participants were followed during the pregnancy period, an average of 9.6 months
- Safety in Children - Number of Subjects (foetuses and newborns) with Adverse Events
  Time frame: Foetuses/Newborns were followed during the pregnancy period, an average of 9.6 months and Follow-Up period (6 weeks after delivery)
- Maternal Safety - Hypoglycaemic episodes
  Time frame: Participants were followed during the pregnancy period, an average of
9.6 months
- Maternal Safety - Nocturnal Hypoglycaemic episodes
  Time frame: Participants were followed during the pregnancy period, an average of 9.6 months
- Maternal Safety - Change in Albumin Serum Level (Biochemistry)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change in Alanine aminotransferase Serum Level (Biochemistry)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change in Alkaline phosphatase Serum Level (Biochemistry)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change in Creatinine Serum Level (Biochemistry)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change in Lactate Dehydrogenase Serum Level (Biochemistry)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change in Potassium Serum Level (Biochemistry)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change in Sodium Serum Level (Biochemistry)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change in Total Protein Serum Level (Biochemistry)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change in Haemoglobin Level (Haematology)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change in Leukocytes Level (Haematology)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)
(FU) Visit (6 weeks after delivery)

- Maternal Safety - Change in Thrombocytes Level (Haematology)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)

- Maternal Safety - Change in Urine Albumin Level (Urinalysis)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)

- Maternal Safety - Change in Albumin/Creatinine Ratio (Urinalysis)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)

- Maternal Safety - Change in Urine N Creatinine (Creatinine) (Urinalysis)
  Time frame: Visit P1 (GW 8-12), Follow-Up (FU) Visit (6 weeks after delivery)

- Maternal Safety - Change in Insulin Detemir Specific Antibodies
  Time frame: Baseline, Visit P4 (GW 36). Baseline is Visit 2 (randomisation visit, within 3 weeks of screening) for subjects not pregnant at randomisation and Visit P1 (GW 8-12) for pregnant subjects at randomisation.

- Maternal Safety - Change in Insulin Aspart Specific Antibodies
  Time frame: Baseline, Visit P4 (GW 36). Baseline is Visit 2 (randomisation visit, within 3 weeks of screening) for subjects not pregnant at randomisation and Visit P1 (GW 8-12) for pregnant subjects at randomisation.

- Maternal Safety - Change in Insulin Detemir/Insulin Aspart Cross Reacting Antibodies
  Time frame: Baseline, Visit P4 (GW 36). Baseline is Visit 2 (randomisation visit, within 3 weeks of screening) for subjects not pregnant at randomisation and Visit P1 (GW 8-12) for pregnant subjects at randomisation.

- Pregnancy Outcome Safety - Level of Detemir Specific Antibodies (AB) in Umbilical Cord Blood
  Time frame: At Delivery (End of Pregnancy)
- Pregnancy Outcome Safety - Level of Aspart Specific Antibodies (AB) in Umbilical Cord Blood
  Time frame: At Delivery (End of Pregnancy)
- Pregnancy Outcome Safety - Level of Cross-Reacting Antibodies (AB) in Umbilical Cord Blood
  Time frame: At Delivery (End of Pregnancy)
- Ratio between Detemir Specific Antibodies in Cord Blood and Maternal Antibodies
  Time frame: At Delivery (End of Pregnancy) and at Visit P4 (GW 36)
- Pregnancy Outcome Safety - Level of Insulin Detemir in Umbilical Cord Blood
  Time frame: At Delivery
- Maternal Safety - Change from Visit P1 in Body Weight During Pregnancy by Visit
  Time frame: Visit P1 (GW (8-12), Visit P2 (GW 14), Visit P3 (GW 24), Visit P4 (GW 36)
- Maternal Safety - Change from Visit P1 in Systolic Blood Pressure During Pregnancy and at Follow-Up by Visit
  Time frame: Visit P1 (GW (8-12)), Visit P2 (GW 14), Visit P3 (GW 24), Visit P4 (GW 36), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change from Visit P1 in Diastolic Blood Pressure During Pregnancy and at Follow-Up by Visit
  Time frame: Visit P1 (GW (8-12)), Visit P2 (GW 14), Visit P3 (GW 24), Visit P4 (GW 36), Follow-Up (FU) Visit (6 weeks after delivery)
- Maternal Safety - Change from Visit P1 in Pulse During Pregnancy and at Follow-Up
  Time frame: Visit P1 (GW (8-12), Visit P2 (GW 14), Visit P3 (GW 24), Visit P4 (GW 36), Follow-Up Visit (6 weeks after delivery)
- Maternal safety - Electrocardiogram (ECG)
  Time frame: Follow-Up (6 weeks after delivery)
- Maternal Safety - Acceleration of Retinopathy in Any Eye
  Time frame: From GW 8-12 (Visit P1) to Follow-Up (6 weeks after delivery)
- Maternal Safety - Acceleration of

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Nephropathy  
Time frame: From GW 8-12 (Visit P1) to Follow-Up (6 weeks after delivery)  
- Maternal Safety - Mode of Delivery  
  Time frame: At Delivery Visit  
- Pregnancy Outcome at Delivery  
  Time frame: Delivery Visit  
- Pregnancy Outcome at Follow-Up  
  Time frame: Follow-Up (6 weeks after delivery)  
- Safety - Total Daily Insulin Dose during Pregnancy  
  Time frame: Visit P2 (GW 14), Visit P3 (GW 24), Visit P4 (GW 36), Follow-Up (6 weeks after delivery)  
- Safety - Composite Pregnancy Outcome  
  Time frame: End of Pregnancy  
- Ratio between Aspart Specific Antibodies in Cord Blood and Maternal Antibodies  
  Time frame: At Delivery (End of Pregnancy) and at Visit P4 (GW 36)  
- Ratio between Cross-reacting Antibodies in Cord Blood and Maternal Antibodies  
  Time frame: At Delivery (End of Pregnancy) and at Visit P4 (GW 36)

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Central contact information

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http://www.novonordisk-trials.com
Trial sponsored by: Novo Nordisk A/S
Contact: clinicaltrials@novonordisk.com
For trials conducted in the US: (+1) 866-867-7178

Labeling Information
- EU:
- US: [link](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/)

Information provided by Novo Nordisk A/S
PDF generation date: 19.Oct.2017

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