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An international non-interventional prospective cohort study to evaluate the safety of treatment with Levemir® (insulin detemir) in pregnant women with diabetes mellitus

Diabetes Pregnancy Registry

Redacted protocol
Includes redaction of personal identifiable information only.

Author:
[redacted], [redacted]
TrialOps-2, Insulin & Devices

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List of abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
BMI	Body Mass Index
CRF	Case Report Form
eCRF	Electronic Case Report Form
DM	Diabetes Mellitus
EDC	Electronic Data Capture
EMA	European Medicines Agency
GPP	Good Pharmacoepidemiology Practice
GW	Gestation Week
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
PSUR	Periodic Safety Update Report
RDS	Respiratory Distress Syndrome
SAE	Serious Adverse Event
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

Glossary

Congenital malformation	A morphological defect of an organ, part of an organ, or larger region of the body resulting from an intrinsically abnormal developmental process
Early foetal death	The death of a foetus before completion of 22 gestational weeks (GW)
Ectopic pregnancy	A pregnancy that occurs outside the uterus
Late foetal death	The death of a foetus after the completion of 22 gestational weeks (GW) including stillbirth
Foetal macrosomia	Birth weight above 4 kg
Large-for gestational age	Live born infant with birth weight > 90th percentile for gestational age and sex according to local reference
Major malformations	A life-threatening structural anomaly or an abnormality likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment. Examples are abnormalities likely to lead to serious handicap or likely to lead to major cosmetic defects (e.g. cleft lip) and which may require major surgery to repair (e.g. atrial septal defect or ventricular septal defect)
Major hypoglycaemia	A hypoglycaemic episode where the patient is not able to treat him/herself and where oral carbohydrates, glucagon or intravenous glucose has to be administered to the patient by another person because of severe central nervous system dysfunction
Minor malformations	Structural anomaly not likely to cause any medical or cosmetic problems
Neonatal death	Death of an infant between 7 days and 28 completed days after delivery
Perinatal death	Death of a foetus/infant between ≥ 22 completed GWs and < 1 completed week after delivery
Pregnancy outcome	The end products of pregnancy which include three main categories: foetal death, spontaneous abortion, and live birth
Pre-term delivery	Delivery before 37 completed gestational weeks
Pre-eclampsia	A condition in pregnancy characterised by new onset of abrupt hypertension (140/90 millimetres of mercury (mm Hg) or greater

	documented on two occasions, at least 6 hours but no more than 7 days apart), and albuminuria
Spontaneous abortion	A naturally occurring termination of a pregnancy before 22 completed gestation weeks. Also called miscarriage

1 Summary

The overall objective of the Diabetes Pregnancy Registry is to monitor and assess the safety of Levemir® use in pregnant women with diabetes mellitus (DM), and to monitor their infants at 1 month and 1 year of age. As a part of the observational data collection, equivalent data will be collected from pregnant women with DM treated with other injectable antidiabetic treatment regimens and their infants until 1 year of age.

A change in type or brand of basal insulin after baseline visit will lead to exclusion from the primary and secondary endpoint analysis, but not from the registry itself. For the primary and secondary objectives comparisons will only be made between women treated with Levemir® and women treated with other basal insulin regimens, who have not changed basal insulin product 4 weeks prior to conception and until delivery/pregnancy termination.

PRIMARY OBJECTIVE:

Pregnancy outcome

Comparison of the proportion of pregnancies in pregnant women who have completed 22 weeks of pregnancy and treated with Levemir® to pregnant women who have completed 22 weeks of pregnancy and treated with other basal insulin regimens which results in none of the following events:

- Major congenital malformations
- Perinatal death
- Neonatal death

Assessed at up to 4 weeks after delivery

KEY SECONDARY OBJECTIVES:

Maternal

Comparison of the following adverse events and abnormal metabolic control in pregnant women treated with Levemir® to pregnant women treated with other basal insulin regimens:

- Incidence of major hypoglycaemic events during the pregnancy period
- Development of pre-eclampsia during pregnancy

Pregnancy outcome

Comparison of pregnancy outcomes in women treated with Levemir® to those treated with other basal insulin regimens with respect to:

- Pre-term delivery
- Spontaneous abortion
- Perinatal death
- Neonatal death

Infants at the age of 1 year

Comparison of, at 1 year of age, the growth and health of infants born to women treated with Levemir® to those born to women treated with other basal insulin regimens.

PRIMARY ENDPOINT:

Comparison of the proportion of pregnancies in pregnant women who have completed 22 weeks of pregnancy and treated with Levemir® to pregnant women who have completed 22 weeks of pregnancy and treated with other basal insulin regimens which results in none of the following events:

- Major congenital malformations
- Perinatal death
- Neonatal death

Assessed at up to 4 weeks after delivery

KEY SECONDARY ENDPOINTS:

Maternal endpoints

- Incidence of major hypoglycaemia during pregnancy
- Proportion of pregnancies complicated by pre-eclampsia during pregnancy

Pregnancy outcome endpoints

- Proportion of pregnancies resulting in perinatal death assessed 1 week after delivery
- Proportion of pregnancies resulting in neonatal death assessed 4 weeks after delivery
- Proportion of pregnancies resulting in spontaneous abortion assessed at pregnancy termination
- Proportion of pregnancies resulting in pre-term delivery assessed at delivery

Infant endpoints at 1 year of age

- Height at the age of 1 year
- Weight at the age of 1 year
- Proportion with changes (progression/regression) of major congenital malformations

For pregnancies with multiple foetuses each foetus will be counted individually for the primary endpoint, the other pregnancy outcome endpoints, and the infant endpoints at 1 year of age.

STUDY DESIGN:

This international, prospective, non-interventional, multi-centre cohort study will monitor and assess the safety of Levemir® use during pregnancy as well as monitor the health status of the infants at 1 month and 1 year of age. The same parameters will also be monitored and assessed for other injectable antidiabetic treatment regimens used during pregnancy. The study period includes the gestation periods of the pregnant women and the follow-up of the infants at 1 month and 1 year of age. The Diabetes Pregnancy Registry has a planned recruitment period of 5 years.

STUDY POPULATION:

Women with DM, who are pregnant and treated with Levemir® or other injectable antidiabetic treatment regimens, and who have not changed basal insulin or other injectable antidiabetic treatment product (for those not treated with basal insulin) 4 weeks prior to and following conception will be included in the Diabetes Pregnancy Registry.

For the statistical analyses only women treated with basal insulin will be included. The group of women treated with Levemir® will be compared to the group of women treated with other basal insulins.

Inclusion criteria

1. Informed consent obtained before any data collection
2. Woman with a positive pregnancy test
3. Diabetes mellitus type 1 or 2, diagnosed prior to conception
4. Currently treated with Levemir® or other injectable antidiabetic treatment(s)
5. Unchanged basal insulin or other injectable antidiabetic treatment product (for those not treated with basal insulin) 4 weeks prior to and following conception

Exclusion criteria

Women who have been pregnant for more than 16 weeks at baseline visit will be excluded from the study.

ASSESSMENTS:

All adverse drug reactions (ADRs) and serious adverse events (SAEs) in pregnant women treated with any injectable antidiabetic treatment regimens, as well as in their off-spring until 1 year of age, should be reported. In addition, pre-eclampsia and major hypoglycaemic events in the pregnant women should be reported regardless of causal relationship and seriousness criteria.

STUDY PRODUCT(S):

Levemir® and other injectable antidiabetic treatment regimens.

2 Flow chart

Flow chart of visits and standard routine procedures.

Visit	**Baseline visit**	**Standard routine visits**	**Delivery visit**	**Follow-up of the infant(s)**	**Follow-up of the infant(s)**
Time of visit	**≤ 16 weeks pregnant**	**Any time during pregnancy [5]**	**Delivery**	**1 month after delivery**	**1 year after delivery**
Visit window				**+ 1 month**	**+ 4 months**
Informed consent	x				
Incl. /excl. criteria	x				
Demographics	x				
Obstetric history	x				
Maternal medical history	x				
Maternal diabetes history	x				
Current antidiabetic treatment	x	x	x		
Concomitant illness	x				
Concomitant medication	x	x	x		
Height [1]	x		x	x	x
Weight [1]	x	x	x	x	x
Vital signs	x	x			
Current pregnancy information	x				
HbA_{1c}	x [2]	x	x		
Major hypoglycaemia		x	x		

Pre-eclampsia		x	x		
ADRs and SAEs [3]		x	x	x	x
Delivery and complications			x		
Pregnancy outcome			x		
Neonatal assessments			x		
Foetal assessments [4]			x		
Neonatal death				x	
Congenital malformations not detected at delivery				x	
Lactation				x	x
Diabetes					x
Changes of major congenital malformations					x

1. Height and weight of the mother during pregnancy and of the infant(s) at delivery, 1 month and 1 year follow-up
2. HbA_{1c} measured ≤ 16 weeks prior to baseline visit is acceptable as baseline visit data (see section 8.1.1)
3. Relevant ADR's and SAE's according to protocol section 9
4. Foetal assessments in case of early termination of pregnancy, perinatal and neonatal death
5. Preferably data from one standard routine visit per month should be entered into the eCRF irrespectively of the number of visits performed

3 Introduction

In this document physician refers to the individual overall responsible for the conduct of the non-interventional study at a study site.

3.1 Basic information

The use of insulin analogues has increased significantly in the treatment of both type 1 and type 2 diabetes mellitus (T1DM and T2DM, respectively). Insulin analogues are used in pregnant women with diabetes, as this group has a particular requirement for the safe and efficacious treatment that insulin analogues can deliver. As pregnancy in women with DM is associated with an increased risk of complications for both the mother and the foetus/new-born especially if glycaemic control is outside the target, and as the treatment needs to be adjusted during pregnancy, it is considered a medical challenge to ensure that these women receive the most optimal glycaemic control without inducing hypoglycaemia. If pregnant women receive optimal treatment, it will both increase their own well-being and reduce the overall risk of diabetes complications and pregnancy complications both for the mother and the child. Complications associated most frequently with pregnancies in women with DM include the following [1-9]:

- Major hypoglycaemia
- Progression of maternal diabetic complications
- Spontaneous abortion
- Pre-eclampsia and pre-term delivery
- Perinatal and neonatal death
- Congenital malformations
- Foetal macrosomia

During recent decades, pregnancy outcomes in women with DM have improved considerably. Hypo- and hyperglycaemia remain, however, a major challenge in the treatment of pregnant women with DM. The proportion of pregnant women reporting major hypoglycaemic episodes that require third party help is as high as 71% [4,6]. Of these, 33−41% of the episodes additionally require parenteral glucose or glucagon.

The rate of pre-eclampsia in pregnancies in women with DM increases with advanced maternal age, poor glycaemic control and baseline proteinuria [1]. The literature is inconsistent in particular with respect to the rate and severity of pre-eclampsia, but the minimum risk reported in women with DM is 10%[10].

The most common organs affected by malformations are the central nervous system, heart, skeleton, kidneys, gastro-intestinal tract and lungs. The prevalence of major congenital anomalies in infants of women with DM was 4.5% in a population-based study in England, Wales and Northern Ireland

[11] and the results are in line with results from a nationwide prospective Norwegian study from 2010 [12]. In addition, infants of women with DM are 5 times more likely to be stillborn and 3 times more likely to die in their first month of life (neonatal death) compared with those of mothers without DM [11]. The perinatal death risk is approximately 3% and the neonatal death risk is 0.9% [11] and comparable with rates from other European countries [11,13-17]. Finally, foetal macrosomia is reported to occur in 25−30% and in some studies in more than 40% of the new-borns to mothers with DM [5,7].

Pregnant women with DM and with good metabolic control are not more likely than non-diabetic women to lose a pregnancy. This is in contrast to a risk of 15−26% of having a spontaneous abortion in the first trimester for diabetic women who have elevated blood glucose levels [3,8,9]. As increased perinatal and neonatal death, morbidity and a 2−5-fold increase in congenital anomalies compared with the general population are reported in pregnant women with DM [2], further data on the effects of treatment on pregnant women with DM are needed.

Levemir® was approved for treatment of pregnant women with DM in the EU in 2011 [18].

3.2 Rationale for the study

As prospective data on the effects of different insulin treatment regimens in general are limited and as no long-term prospective epidemiological studies examining safety in pregnant women with DM and pregnancy outcomes have been conducted, a diabetes pregnancy registry including such prospective data is highly warranted.

Novo Nordisk A/S will establish an international Diabetes Pregnancy Registry to monitor the safety of the use of Levemir® and other injectable antidiabetic treatment regimens in pregnant women during the gestational period and to monitor their infants at the age of 1 year. The present registry constitutes a unique opportunity for large-scale data collection that will allow comparisons and analysis between the various insulin treatment regimens in pregnant women with DM.

All data collection and statistical analysis will be done in accordance with global and local regulations and legal data protections requirements.

4 Objectives and endpoints

4.1 Objective(s)

The overall objective of the Diabetes Pregnancy Registry is to monitor and assess the safety of Levemir® use in pregnant women with DM, and to monitor their infants at 1 month and at 1 year of age. As a part of the observational data collection, equivalent data will be collected from pregnant women with DM treated with other injectable antidiabetic treatment regimens, and their infants at 1 month and at 1 year of age.

For the primary and secondary objectives comparisons will only be made between women treated with Levemir® and women treated with other basal insulin regimens, who have not changed basal insulin product 4 weeks prior to conception and until delivery/pregnancy termination.

4.1.1 Primary objective

Pregnancy outcome

Comparison of the proportion of pregnancies in pregnant women who have completed 22 weeks of pregnancy and treated with Levemir® to pregnant women who have completed 22 weeks of pregnancy and treated with other basal insulin regimens which results in none of the following events:

- Major congenital malformations
- Perinatal death
- Neonatal death

Assessed at up to 4 weeks after delivery.

4.1.2 Secondary objective

Maternal

Comparison of the following adverse events and abnormal metabolic control in pregnant women treated with Levemir® to pregnant women treated with other basal insulin regimens:

- Incidence of major hypoglycaemic events during the pregnancy period
- Development of pre-eclampsia during pregnancy
- Metabolic control measured as HbA_{1c} during pregnancy

Pregnancy outcome

Comparison of pregnancy outcomes in women treated with Levemir® to those treated with other basal insulin regimens with respect to:

- Foetal macrosomia
- Large-for gestational age
- Pre-term delivery
- Spontaneous abortion
- Induced abortion due to major congenital malformations (by organ)
- Perinatal death
- Neonatal death
- Live birth with major congenital malformations(by organ)
- Live birth with minor congenital malformations(by organ)

Infants at the age of 1 year

Comparison of, at 1 year of age, the growth and health of infants born to women treated with Levemir® to those born to women treated with other basal insulin regimens.

4.2 Endpoints

4.2.1 Primary endpoints

Comparison of the proportion of pregnancies in pregnant women who have completed 22 weeks of pregnancy and treated with Levemir® to pregnant women who have completed 22 weeks of pregnancy and treated with other basal insulin regimens resulting in none of the following events:

- Major congenital malformations
- Perinatal death
- Neonatal death

Assessed at up to 4 weeks after delivery.

4.2.2 Secondary endpoints

4.2.2.1 Maternal endpoints

- Incidence of major hypoglycaemia during pregnancy
- Proportion of pregnancies where the woman experiences at least one major hypoglycaemic event during pregnancy
- Proportion of pregnancies complicated by pre-eclampsia during pregnancy
- HbA_{1c} level assessed as close as possible to conception, end of first trimester, end of second trimester, and at delivery.

4.2.2.2 Pregnancy outcome endpoints

- Proportion of pregnancies resulting in perinatal death assessed at 1 week after delivery
- Proportion of pregnancies resulting in neonatal death assessed at 4 weeks after delivery
- Proportion of pregnancies resulting in live birth with major congenital malformations and by organ assessed at delivery
- Proportion of pregnancies resulting in live birth with minor congenital malformations and by organ assessed at delivery
- Proportion of induced abortions due to major congenital malformations and by organ assessed at delivery
- Proportion of pregnancies resulting in spontaneous abortion assessed at pregnancy termination
- Proportion of pregnancies resulting in live birth with foetal macrosomia assessed at delivery
- Proportion of pregnancies resulting in live born infants with birth weight > 90th percentile for gestational age and sex (local reference) assessed at delivery
- Proportion of pregnancies resulting in pre-term delivery assessed at delivery

4.2.2.3 Infant endpoints assessed at 1 year of age

- Height at the age of 1 year
- Weight at the age of 1 year
- Proportion with DM
- Proportion with changes (progression/regression) of major congenital malformations

For pregnancies with multiple foetuses each foetus will be counted individually for the primary endpoint, the other pregnancy outcome endpoints, and the infant endpoints at 1 year of age.

5 Study design

5.1 Type of study

This study is a post-authorisation commitment to the European Medicines Agency – a Post Authorisation Safety Study (PASS) - to monitor the long-term safety of Levemir® in pregnant women to cover the gestation and lactation. This international, prospective, non-interventional, multi-centre cohort study will monitor and assess the safety of Levemir® use during pregnancy as well as monitoring the health status of the infants at 1 month and at 1 year of age. The same parameters will also be monitored and assessed for other injectable antidiabetic treatment regimens.

The study is non-interventional as the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study.

Enrolment of women on injectable antidiabetic treatment regimens will most likely also include women treated with injectable antidiabetic drugs apart from insulins. Treatment with such injectable antidiabetic drugs for example GLP-1 agonists during pregnancy is off-label use. Due to the non-interventional study design of the Diabetes Pregnancy Registry women treated with injectable antidiabetic drugs other than insulins will be included either if they are treated with other injectable antidiabetic drugs solely or treated with a combination of insulin and other injectable antidiabetic drugs. The information on all insulins and other injectable antidiabetic treatment regimens is collected for the completeness of the non-interventional real-world data collection in order to obtain a comprehensive overview of the treatment patterns used in pregnant women with DM.

Change in dosage, dose interval and add-on or removal of bolus insulin, oral antidiabetic drugs and/or GLP-1 agonists is expected and will not exclude pregnant women to participate in the registry and in the primary and secondary endpoint analysis. A change in type or brand of basal insulin after baseline visit will lead to exclusion from the primary and secondary endpoint analysis, but not from the registry itself.

The study period includes the gestation periods of the pregnant women and the follow-up of the infants at 1 month and at 1 year of age.

5.2 Rationale for study design

The Diabetes Pregnancy Registry is specifically designed to monitor and assess the safety of the use of Levemir® in pregnant women and the health status of their infants until 1 year of age. Every diabetic woman treated with insulin or other injectable antidiabetic treatment regimens and who has not changed basal insulin or other injectable antidiabetic treatment product (for those not treated with basal insulin) 4 weeks prior to and following conception is eligible for enrolment. Thus, the

registry constitutes a unique opportunity for large-scale data collection that will allow comparisons and analysis between the injectable antidiabetic treatment regimens in pregnant women with DM.

The Diabetes Pregnancy Registry will be based on prospectively collected clinical data as part of the normal clinical practise in pregnancy. The database will be established as part of present standard clinical practice used in the treatment of pregnant women with DM at the selected study sites. A panel of the study sites enrolled in the Novo Nordisk Levemir® pregnancy trial (NN304-1687) were contacted prior to inclusion in the registry, and asked to fill out a flow chart illustrating the specific standard routine procedures at their specific clinic. The standard routine procedures used with regard to the treatment of diabetic women during pregnancy are almost similar between the included study sites resulting in a uniformed treatment procedure and furthermore, these study sites have a relatively high prescription rate of Levemir®.

The prospective non-interventional study design in a large-scale setting is needed to ensure a sufficient number of patients in order to have an adequately powered study to analyse the safety of Levemir® with regard to the primary and secondary endpoints in a real-world population of diabetic pregnant women and their infants.

The collected data will constitute the Diabetes Pregnancy Registry data set.

5.3 Treatment of patients

Patients will be treated according to routine clinical practice at the discretion of the treating physician.

5.4 Limitation of study design and data sources

Due to the exploratory nature of the study, the results will contribute to the current knowledge regarding treatment of pregnant women with both insulins and other injectable antidiabetic treatment regimens. A substantial high number of patients in the registry will enable confirmation of existing evidence from clinical studies and a generation of new hypotheses with respect to the long-term safety of Levemir® and other injectable antidiabetic treatment regimens in pregnant women with DM and their infants.

A heterogeneous patient population and different local requirements with regard to the routine patient management may limit the explanatory power of the study results if not well-adjusted in the analysis part. Heterogeneity will, however, be minimal in the present registry as the study sites have many similarities with regard to standard routine procedures in the treatment of pregnant women with DM. Confounding factors and other relevant background covariates will be collected at the baseline visit in order to adjust for relevant factors in the statistical analysis.

Results from statistical analysis may be biased if not all pregnancies are registered in the Diabetes Pregnancy Registry, particularly if data is only entered when the patient experiences an ADR/SAE. In order to minimise the risk of such bias the physician must ensure that all registered pregnancies regardless of treatment regimens in the specific clinic are enrolled in the Diabetes Pregnancy Registry unless the women do not want to participate (do not sign the informed consent form).

6 Study population

Women with DM, who are pregnant and are treated with Levemir® or other injectable antidiabetic treatment regimens, will be invited to participate in the Diabetes Pregnancy Registry. In order to obtain as much information as possible within an appropriate timeframe, women who have a positive pregnancy test, are diagnosed with DM prior to conception, and who have not changed basal insulin or other injectable antidiabetic treatment product (for those not treated with basal insulin) 4 weeks prior to and following conception will be included in the Diabetes Pregnancy Registry.

6.1 Number of patients to be studied

Estimated number of patients to be included during the recruitment period: minimum: 2,037

Recruitment will close once it is secured that 611 patients treated with Levemir® are eligible for the primary analysis.

Based on sample size calculations (Section 14) the number of pregnancies needed for the primary endpoint calculations is 1,222 pregnancies with information on the primary endpoint pregnancy outcomes:

- perinatal death
- neonatal death
- liveborn infant with 1 month follow up (irrespective if there is a malformation or not)

Liveborn infants will be followed up until 1 year with the aim of collecting data for the secondary endpoints.

It is expected that approximately 60% of the included pregnancies will be fulfilling the criteria for primary endpoint calculations, as 40 % are assumed to be excluded or used for secondary endpoints. These 40% of subjects are assumed to consist of subjects who experience one or more of the following: abortion (spontaneous or induced), change in basal insulin treatment, treatment with other antidiabetic treatment regimens, or lost to follow-up.

Therefore, it is calculated that a minimum of (1,222/60*100) 2,037 patients are to be included in the study.

Note that the study plans to include a minimum of 2,037 patients treated with injectable antidiabetic treatment regimens, but that only women treated with Levemir® and other basal insulins will be included in the primary analyses.

6.2 Inclusion criteria

For an eligible patient, all inclusion criteria must be answered "yes".

1. Informed consent obtained before any data collection
2. Woman with a positive pregnancy test
3. Diabetes mellitus type 1 or 2, diagnosed prior to conception
4. Currently treated with Levemir® or other injectable antidiabetic treatment(s)
5. Unchanged basal insulin or other injectable antidiabetic treatment product (for those not treated with basal insulin) 4 weeks prior to and following conception

An eligible woman may be included in the Diabetes Pregnancy Registry more than once, should the pregnancies occur within the recruitment period.

6.3 Exclusion criteria

Women who have been pregnant for more than 16 weeks at baseline visit will be excluded from the study.

6.4 Withdrawal criteria

Patients may withdraw at will at any time, for any reason.

6.5 Rationale for study population

The Diabetes Pregnancy Registry is a non-interventional epidemiological study where data are collected on standard routine procedures. The results and observations from the registry will, hence, be more broadly applicable to the real-world population of pregnant women with DM, and their infants than study populations enrolled in a typical randomised controlled trial.

Only women with either T1DM or T2DM who are treated with Levemir® or other injectable antidiabetic treatment regimens and who have not changed basal insulin or other injectable antidiabetic product (for those not treated with insulin) 4 weeks prior to and following conception will be included. During the pregnancy the women attend regular visits to specialist clinics for the treatment of their DM and therefore, it is optimal to contact experienced clinics with a high number of potential candidates.

Gestational DM has been excluded because the women may not develop the disease until late in pregnancy, where the organogenesis is finalized and thereby the risk of malformation significantly reduced. Furthermore, at least a fraction of these may control the gestational DM by diet alone.

7 Study schedule

Timelines may be adjusted during the course of the present non-interventional study.

Planned date for first patient first visit: Q3 2013

Estimated completion of the last patient (last patient last visit, LPLV): Q2 2020

The end of the non-interventional study is defined as LPLV

Planned completion of non-interventional study report: Study progress reports will be submitted to the participating clinics and the European Medicines Agency (EMA) on an annual basis. This study is subject to registration no later than 21 days after enrolment of the first study participant according to a Novo Nordisk A/S requirement on non-interventional study disclosure. Only the main study site per country will be disclosed via facility name, city and country on the study registration.

Note: Study registration is regarded as the publication of an internationally-agreed set of information about the design, conduct and administration of clinical trials. These details are published on a publicly-accessible website managed by a registry conforming to World Health Organization (WHO) standards (e.g. www.clinicaltrials.gov and www.encepp.eu).

All physicians will be notified by Novo Nordisk A/S immediately when the recruitment period comes to an end, after which no patients must be enrolled.

8 Methods and assessments

The Diabetes Pregnancy Registry will include maternal and paediatric assessments as per standard practise. There are differences in the endpoints covering the gestation period, the delivery, the pregnancy outcomes, the postpartum visit and the follow-up in the infants. The variables on the study forms will depend on these different endpoints.

All parameters which will be collected in this registry are defined in accordance with normal clinical practice. Relevant registry forms for the baseline visit including potential confounders, standard routine visits, delivery visit, the postpartum visit and the follow-up of the infants are developed together with some of the study sites participating in the registry.

Signed informed consent must be obtained prior to any data entry into the registry.

After the Informed Consent Form has been signed, patients will be allocated an ID number, which will remain unchanged throughout the study. The physician will assign each enrolled patient with a unique 6 digit patient number. The patient number is composed of 3 digits unique for each study site followed by 3 consecutive digits for each enrolled patient on the study site. If an eligible woman is included in the Diabetes Pregnancy Registry more than once, she will be allocated a new patient ID number for each pregnancy that may occur during the recruitment period The infant(s) of the patient will be allocated the same ID number as its mother followed by a “Xn” at the end of the 6 digit patient number (n=1, 2, 3 and so forth for each child).

Patients enrolled in the study will be provided with contact address and telephone number of the physician site and/or staff.

In case a patient is withdrawn from the study the physician will ensure that the primary reason for discontinuation will be specified in the eCRF.

This section describes the general study procedures applicable for all patients. Visit and contact specific procedures are described in sub-sections below.

8.1 Visit procedures

An eCRF should be completed for all patients.

The standard, routine treatment of the individual patients enrolled into the registry should not be influenced by or interfered with following recruitment. Therefore the data collected is only what is collected as part of standard routine and missing data is expected. All data collected at the visits is data from standard routine procedure visits and the frequency of these visits is determined by the individual study site. The delivery information and the information collected at 1 month and at 1

year follow-up are not necessarily standard procedures, but the data collected will be part of standard routine assessments.

The physician must keep a patient enrolment log throughout the enrolment period.

8.1.1 Baseline visit

Signed informed consent must be obtained before any data recording is performed for the purpose of this non-interventional study.

The following will be performed at the baseline visit which will occur as soon as the woman has discovered her pregnancy through a positive pregnancy test:

- Check of eligibility against inclusion criteria (section 6.2)
- Check whether the patient has previously participated in the registry (if yes, please state previous patient ID number)
- Demographics (section 8.3.1)
- Obstetric history (section 8.3.2)
- Maternal medical history (section 8.3.3)
- Maternal diabetes history (section 8.3.3)
- Current insulin and/or injectable antidiabetic treatment and/or OAD use (section 8.3.3)
- Concomitant illnesses (section 8.3.4)
- Concomitant medication (section 8.3.4)
- Anthropometric measurements (section 8.3.5)
- Vital signs (section 8.3.6)
- Current pregnancy (section 8.3.7)
- HbA_{1c} level assessed according to standard routine at local laboratories (HbA_{1c} level measured $\leq$ 16 weeks prior to baseline visit is acceptable as baseline visit data)

8.1.2 Standard routine visits

The standard routine practice covers all visits to the clinic after the baseline visit. These visits may differ in frequency between the study sites. Preferably data from one standard routine visit per month should be entered into the eCRF irrespective of the number of visits performed. The following information should, however, be recorded at each standard routine visit, if available:

- Weight measurement (section 8.3.5)
- HbA_{1c} level assessed according to standard routine at local laboratories
- Current insulin and/or injectable antidiabetic treatment and/or OAD use, only required if the type of insulin or product has changed since last visit (section 8.3.3)
- Change in concomitant medication (section 8.3.4)

- Vital signs (section 8.3.6)
- Major hypoglycaemic events since last visit (section 8.3.8)
- Congenital malformations in the foetus
- ADRs, SAEs, and all major hypoglycaemic episodes and pre-eclampsia since last visit (section 9)

8.1.3 Delivery

Relevant information during labour and delivery and neonatal assessment will be documented in the eCRF.

During labour and delivery, the use of insulin and glucose will be according to local practice.

The following will be recorded in the eCRF:

8.1.3.1 Mother/foetus

- Early or late foetal death including spontaneous or induced abortion must be reported in the eCRF (section 8.3.12) and as SAEs (section 9.1)
- Insulin and/or injectable antidiabetic treatment and/or OAD use during delivery, only if the type of insulin or product has changed since last visit (section 8.3.3)
- Change in concomitant medication (section 8.3.4)
- ADRs, SAEs, major hypoglycaemic episodes and pre-eclampsia since the last visit (section 9)
- Delivery information (section 8.3.10)
- HbA1c level assessed according to standard routine at local laboratories

8.1.3.2 Neonate

Details on pregnancy outcome/neonatal assessment will be entered in the eCRF (section 8.3.11)

If the infant has any congenital anomaly/birth defect observed at examination this must be reported, recorded and followed up as a SAE according to section 9.1 and 9.2.

If the neonate has experienced any ADRs or SAEs, these should be reported.

8.1.4 Post partum visit

The postpartum visit will be a 1 month follow-up data collection of the infants to the women with an allowed visit window of +1 month. The follow-up will be performed as a questionnaire sent to the women and will be followed up with a telephone interview of the women. The date of visit to be entered in the eCRF should be the date where the body measurements were performed. It is not

mandatory to collect the completed questionnaires. The following information will be asked in the questionnaire:

- Height at the age of 1 month (approximately)
- Weight at the age of 1 month (approximately)
- Neonatal death of the infant (y/n)
- Congenital malformations (minor/major) not detected at delivery
- Duration of exclusive lactation and/or duration of partial lactation (section 8.3.13)
- If the neonate has experienced any AEs, only ADRs and SAEs should be reported in the eCRF

8.1.5 End of study visit

The end of study visit will be a 1 year follow-up data collection of the infants to the women with an allowed visit window of +4 months. The follow-up will be performed as a questionnaire sent to the women with infants and will be followed up with a telephone interview of the women with infants. The following information will be asked in the questionnaire:

- Height at the age of 1 year (approximately)
- Weight at the age of 1 year (approximately)
- Duration of exclusive lactation and/or duration of partial lactation (section 8.3.13)
- Diabetes in the infants (y/n)
- Changes (progression/regression) of major congenital malformations
- If the infant has experienced any AEs, only ADRs and SAEs should be reported in the eCRF

8.2 Assessments for safety

All ADRs and SAEs in pregnant women treated with any injectable antidiabetic treatment regimens, as well as in their off-spring until 1 year of age, should be reported. In addition, pre-eclampsia and major hypoglycaemic events in the pregnant women should be reported regardless of causal relationship and seriousness criteria. Please see section 9 for definitions and further detail.

If any additional safety reporting is required by local laws and/or Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), these should be complied with.

The physician will ask the pregnant woman participating during each visit if she has encountered any AEs or if she has experienced any hospitalisations or other SAEs. This may be done by posing a simple question such as “have you experienced any problems since the last visit/contact?” All ADRs and SAEs according to section 9 will be recorded in the eCRF.

All safety data collected regarding Levemir® treatment and other Novo Nordisk A/S products for pregnant women will be reviewed periodically and reported in the PSURs to EMA.

8.3 Other assessments

8.3.1 Demographics

The following maternal information will be recorded at baseline visit:

- Date of birth
- Race
- Socioeconomic status (education, occupation)
- Recreational drug use
    - Tobacco (y/n, how much/day)
    - Alcohol (y/n, how much/day)
    - Other (y/n, how much/day)

8.3.2 Obstetric history

The following will be recorded at baseline visit:

- Previous pregnancies and outcome:
    - Number of previous pregnancies
    - Number of previous live birth
    - Previous pregnancy complications (y/n)
        - Pre-eclampsia
        - Caesarean section(s)
        - Perinatal death(s)
        - Preterm delivery(ies)
        - Spontaneous abortion(s)
        - Malformations (major/minor, by organ)

8.3.3 Maternal medical history

The following will be recorded at baseline visit:

- Medical history:
    - Hypertension (y/n)
    - Epilepsy (y/n)
    - Thyroid disorder (y/n)
    - Asthma (y/n)
    - Heart disease (y/n)

- Psychiatric disorders (y/n)
- Inheritable diseases (if yes, specify)
- Other concomitant illnesses (y/n)

- Concomitant medication (section 8.3.4)
- Diabetes mellitus history:
  - Type of DM (T1DM or T2DM)
  - Date of diagnosis of diabetes. If no specific date is available, an approximate date should be entered
  - Date of diagnosis of diabetic complications, if any (according to standard procedure). If no specific date is available, an approximate date should be entered.
    - Retinopathy
    - Neuropathy
    - Nephropathy
    - Macroangiopathy (including peripheral vascular disease) (y/n)
    - Acute myocardial infarction (y/n)
    - Unstable angina (y/n)
    - Heart failure (y/n)
- Current insulin or other injectable antidiabetic treatment:
  - Duration of treatment with insulin, OADs and/or other injectable antidiabetic drugs
  - Start date of current treatment with insulin, OADs and/or other injectable antidiabetic drugs. If no specific date is available, an approximate date should be entered
  - Type, name and dose of current insulin, OADs and/or other injectable antidiabetic drugs

8.3.4 Concomitant illnesses and medication

Concomitant illness

Any illness that is present at the start of the study (i.e. at the baseline visit) including any pre-planned procedures/surgeries, and any intermittent illness that may not be present at the time of this visit.

For each concomitant illness, date of onset should be recorded. If no specific date is available, an approximate date should be entered.

Concomitant medication

Details of all concomitant illnesses must be recorded at the baseline visit. Details of all concomitant medication that is expected to continue during pregnancy must be recorded at the baseline visit. Any changes in concomitant medication up to or equal to 16 weeks must be recorded.

The information collected for each concomitant medication includes start date, stop date or continuing, and indication.

Furthermore information regarding concomitant medication will be collected in the following cases:

- During pregnancy and delivery in case of ADRs, SAEs, major hypoglycaemic episodes and pre-eclampsia
- For the infants in case of ADRs and SAEs
- For both the mother and the infant in case the infant is experiencing an ADR or a SAE and is lactating

8.3.5 Maternal anthropometric measurements

Height (without shoes) will be measured at the baseline visit. Height is measured in metres (m) and recorded with 2 decimals.

Body weight will be measured at the baseline visit and every study visit until delivery. Body weight is measured without shoes, wearing light clothing. Body weight will be recorded in kilograms (kg) with one decimal.

Body mass index (BMI; kg/m^2) will be calculated as weight (kg) divided by height (m) squared in the eCRF.

8.3.6 Vital signs

At each visit the diastolic and systolic blood pressure and pulse will be measured according to standard procedures.

8.3.7 Current pregnancy

The following information will be recorded at the baseline visit:

- Age at conception
- Date of first day of last menstrual period
- GW based on ultra sound scan
- Folic acid taken before and during first trimester (y/n)

8.3.8 Major hypoglycaemic events

Major hypoglycaemia is defined as a hypoglycaemic episode where the patient is not able to treat him/herself and where oral carbohydrates, glucagon or intravenous glucose has to be administered to the patient by another person because of severe central nervous system dysfunction.

The woman will be asked at any visit/contact whether she has experienced any major hypoglycaemic events since last study visit/contact (y/n and if yes how many). These events should be reported according to section 9.

8.3.9 Pre-eclampsia

Pre-eclampsia is defined as a condition in pregnancy characterised by new onset of abrupt hypertension (140/90 millimetres of mercury (mm Hg) or greater documented on two occasions, at least 6 hours but no more than 7 days apart), and albuminuria.

In case of pre-eclampsia this will be reported in the eCRF and according to section 9.

8.3.10 Delivery information

The following details of delivery and complications, if any, will be recorded at the delivery:

- Spontaneous onset of labour (y/n)
- Induction of labour (y/n)
- Vaginal (spontaneous/instrumental delivery)
    - If instrumental, the reason:
        - Foetal distress
        - Lack of progression
        - Other
- Caesarean section (y/n)
    - If yes: report indication for caesarean section
        - Planned caesarean section
        - Non-planned caesarean section

8.3.11 Pregnancy outcome/Neonatal assessments

At the delivery visit, the following details regarding the pregnancy outcome/neonate will be recorded in the eCRF:

- Date of birth/outcome
- Time of birth
- Live birth (y/n)
- GW at birth (completed weeks + days)
- Physical examination, including:
    - Length and head circumference at birth (measured in cm with one decimal)
    - Birth weight (measured in grams)
- Gender (male/female)
- Conditions at birth, including

- Apgar score at 5 minutes
- Admission to intensive care unit for more than 48 hours (y/n)
  - Reason
  - Length of stay (days)
  - Treatment

Neonatal illness

- Arterial umbilical cord pH
- Birth injury (fractures/nerve injury) (y/n)
- Respiratory distress syndrome (RDS), (i.e. chest X-ray consistent with RDS) (y/n)
  - Treatment with nasal continuous positive airway pressure (CPAP)
  - Treatment with surfactant treatment
  - Treatment with ventilator
- Neonatal hypoglycaemia (defined as plasma glucose ≤ 1.7 mmol/l (31mg/dl) during the first 24 hours (y/n)
- Neonatal hypoglycaemia after 24 h.− 48 h. plasma glucose values ≤ 2.5 mmol/l (45 mg/dl)) (y/n)
- Malformations (y/n)
- If yes, minor/major malformations by organ
- Other reasons

8.3.12 Foetal assessments (in case of early termination of pregnancy, early foetal death and perinatal death) and neonatal death

The following details regarding foetal/infant death will be recorded at the pregnancy outcome page in the case report form (CRF):

- Induced abortion (interruption of a living pregnancy < 22 completed weeks)
- Spontaneous abortion
- Ectopic pregnancy
- Perinatal death
- Neonatal death
- GW at termination
- Malformations (y/n)
- If yes, minor/major malformations by organ
- Other relevant information (e.g. autopsy) (y/n)

8.3.13 Lactation

The lactation period will be defined as the period with exclusive lactation, (i.e. the infant is only fed breast milk) and the period with partial lactation, (i.e. the infant is still fed breast milk but also receive other nourishment (formula and/or solid food)).

9 Reporting of safety information

In this study, the following safety information will be systematically collected:

All ADRs and SAEs in the pregnant women participating in the study, as well as in their off-spring until 1 year of age. In addition, pre-eclampsia and major hypoglycaemic events in the pregnant women should be reported regardless of causal relationship and seriousness criteria. Early and late foetal death including spontaneous and induced abortions should be reported as SAEs.

The primary objective of this trial is to monitor the safety of Levemir® in pregnant women with diabetes and their infants until 1 year of age. However, as other injectable antidiabetic treatment regimens may be used, Novo Nordisk A/S will also collect safety data related to these treatments.

Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient administered with a product, which does not necessarily have a causal relationship with the product.

Adverse drug reaction

An adverse drug reaction (ADR) is an untoward medical occurrence in a patient administered or using a product for which a causal relationship between the product and the occurrence is suspected, i.e. judged possible or probable (for definitions, see below) by the reporter or by Novo Nordisk.

An ADR can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, which is considered related to the product.

Terms used to describe causal relationship

- Probable: good reasons and sufficient documentation to assume a causal relationship
- Possible: a causal relationship is conceivable and cannot be dismissed
- Unlikely: the event is most likely related to an aetiology other than the study product

Seriousness criteria

An adverse event is a **serious adverse event**, if the event results in any of the following seriousness criteria:

- Death
- A life-threatening [a] experience
- In-patient hospitalisation or prolongation of existing hospitalisation [b]
- A persistent or significant disability/incapacity [c]
- A congenital anomaly/birth defect

- Important medical events that may not result in death, be life-threatening [a] or require hospitalisation [b] may be considered a serious adverse event - when based upon appropriate medical judgement - they may jeopardise the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition [d]

[a] The term "life threatening refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

[b] The term "hospitalisation" is used when a patient is: admitted to a hospital/inpatient (irrespective of the duration of physical stay), or not admitted to a hospital/not inpatient, but stays at the hospital for treatment or observation for more than 24 hours. Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, study related and social purposes do not constitute adverse reactions or events and should therefore not be reported as adverse reactions or events including serious adverse reactions or events. Likewise, hospital admissions for surgical procedures planned prior to study inclusion are not considered adverse reactions or events including serious adverse events or reactions. Excluded is also hospitalisation due to caesarean section, however if the reason for a caesarean section fulfils the criteria of an SAE (e.g. placenta rupture or pre-eclampsia) the reason should be reported as a serious adverse event. If the off-spring is hospitalised only due to maternal delivery/post-delivery complications, no SAE should be reported for the off-spring.

[c] A substantial disruption of a patient's ability to conduct normal life functions, (e.g. following the event or clinical investigation the patient has significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life).

[d] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Non-serious adverse event

An adverse event that does not meet a seriousness criterion is considered to be non-serious.

Severity assessment definitions

- Mild – No or transient symptoms, no interference with the patient's daily activities
- Moderate - Marked symptoms, moderate interference with the patient's daily activities
- Severe - Considerable interference with the patient's daily activities, unacceptable

Outcome categories and definitions

- Recovered - The patient has fully recovered from the condition, or by medical or surgical treatment the condition has returned to the level observed at the first study related activity after the patient has signed the informed consent
- Recovering - The condition is improving and the patient is expected to recover from the condition/event
- Recovered with sequelae - The patient has recovered from the condition, but with a lasting effect due to a disease, injury, treatment or procedure. If the sequelae meet a seriousness criterion, the adverse reaction or adverse event must be reported as a serious adverse reaction or serious adverse event
- Not recovered - The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting
- Fatal - (only applicable if the patient died from a condition related to the reported adverse reaction or adverse event. Outcomes of other reported adverse reaction or adverse event in a patient before he/she died should be assessed as "recovered", "recovering" or "not recovered". An adverse reaction or adverse event with fatal outcome must be reported as a serious adverse reaction or serious adverse event)
- Unknown - This term should only be used in cases where the patient is lost to follow-up

9.1 Collection, recording and reporting of adverse events

The patient will be asked about adverse events at each visit/contact during pregnancy. Example: "Have you experienced any problems since our last contact?"

At the follow-up visits of the infant at one month and one year after delivery, the mother will be asked about adverse events in the child (e.g. "Has your child experienced any health problems since the last visit?").

All serious adverse events must be reported by the physician to Novo Nordisk A/S within the following timelines:

- Initial information must be reported on the AE form in the eCRF - **within 24 hours of the physician's knowledge of the event**
- For each SAE a safety information form in the eCRF should be completed in addition to the AE form **within 5 calendar days of the physician's knowledge of the event**
- If the initial reporting was made by any other means (e.g. phone call within 24 hours), the initial and further safety information must be provided in the eCRF within 5 calendar days of the physician's knowledge of the event

All non-serious ADRs must be reported by the physician to Novo Nordisk A/S within 60 days after a visit/contact with the patient.

The physician must complete the forms for systematically collected events within the above specified timelines of obtaining knowledge about the event(s). For SAEs the physician must sign the form within 7 days after completing after the form. All non-serious ADRs must be recorded by the physician on the AE form, and each SAE must be recorded on a safety information form (SIF) in the eCRF in addition to the AE form. All AEs, either observed by the Physician or reported by the patient, must be evaluated by the Physician. Sponsor's assessment of expectedness is done according to the reference documents:

Novo Nordisk A/S marketed products: Summary of Product Characteristics, current version for countries in EU and National Product Information, current version for countries outside EU.

Sponsor does not evaluate expectedness and causality of non Novo Nordisk A/S marketed products (injectable antidiabetic drug). Events evaluated as related to non-Novo Nordisk products by Investigator will be reported to the relevant Marketing Authorisation Holder by Novo Nordisk.

The physician should record the diagnosis, if available. If no diagnosis is available the physician should record each sign and symptom as individual adverse events. When a diagnosis becomes available the diagnosis should be reported and the signs and symptoms covered by the diagnosis should be described.

If more than one sign or symptom is to be reported, use a separate form for each sign and symptom. However, if several symptoms or diagnosis occur as part of the same clinical picture only one safety information form can be used to describe all the adverse events.

The sponsor must inform the local regulatory authorities and Independent Ethics Committee (IECs)/ Institutional Review Board (IRBs) in accordance with the local requirements in force and Good Pharmacoepidemiology Practice (GPP) of any serious ADRs related to Novo Nordisk study products.

The sponsor will notify the physician of any serious ADRs related to Novo Nordisk study products, in accordance with the local requirements.

9.2 Follow-up of adverse events

Follow-up information should only include new (corrections or new or additional) information concerning previously reported serious adverse events and must be reported by the physician **within 24 hours** of the physician's knowledge of the follow-up information in the AE form and the Safety Information Form in the eCRF.

Follow-up information concerning previously reported non-serious ADRs must be reported by the physician on the AE form in the eCRF as soon as possible, and no later than 60 days after the physician's knowledge of the follow-up information.

All follow-up information requested by Novo Nordisk A/S must be forwarded to Novo Nordisk A/S within 14 calendar days from the date specified on the request, unless otherwise specified in the follow-up information request.

The physician must ensure that the worst case severity and seriousness is kept consistent through the series of forms used for safety reporting. The follow up information should only include new (updated and/or additional) information that reflects the situation at the time of the physician's signature.

All reported events must be followed until the outcome is "recovered", "recovered with sequelae" or "fatal" and until all queries have been resolved. Cases of chronic conditions, cancer, serious adverse events ongoing at the time of the death (i.e. the patient dies from another serious adverse event) can be closed with the outcome of "recovering" or "not recovered". Cases can be closed with an outcome of "recovering" when the patient has completed the post-study follow-up period (as stated in this protocol) and is expected by the physician to recover.

9.3 Safety committee(s)

9.3.1 Internal Novo Nordisk safety committee

The Novo Nordisk A/S internal Insulin Detemir safety committee will perform ongoing safety surveillance.

10 Electronic Case Report Forms

Novo Nordisk A/S will provide a system for Electronic Data Capture and eCRFs will be provided as a web-based solution.

This system and support services to the system will be supplied by a vendor. The activities of this vendor will be under the direction and supervision of Novo Nordisk A/S.

10.1 Rules for completing eCRFs

Ensure that the eCRF is as complete as possible.

If a test/assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable) indicate this according to the instructions for completing eCRFs.

By signing the case book electronically, the physician confirms that the information is complete and correct.

10.2 Corrections to eCRFs

eCRF data can be corrected only by the physician or the physician's authorised staff. An audit trail will be maintained in the EDC application containing as a minimum: identification of the person entering the data, date and time of the entry and reason for the correction, the original entry and the corrected entry.

If corrections are made by the physician's authorised staff after the date of the physician's signature on the case book, the case book must be signed again by the physician.

10.3 eCRF Flow

The physician must ensure that data is recorded in the eCRFs as soon as possible after the visit. When data is entered it will be available to Novo Nordisk A/S for data verification activities.

When the final non-interventional study report is available the data will be archived by Novo Nordisk A/S.

11 Supervision procedures

During the course of the study, the supervisor should visit the study site to ensure that the protocol has been adhered to and that all issues and data have been recorded.

The supervisor must ensure that the eCRFs are completed.

12 Data management

Data management is the responsibility of Data Management, Novo Nordisk A/S Headquarters. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk A/S or to a contract research organisation (CRO).

Each patient and infant will be identified by a patient number, see section 8. The physician or qualified staff enter the data by using the electronic CRFs. Data managers, who are responsible for the Diabetes Pregnancy Registry Database, follow up on the data flow and prepare periodical reports to be communicated to Novo Nordisk A/S and clinics participating in the registry to ensure correctness of data. Appropriate measures such as encryption or deletion must be enforced to protect the identity of human patients in all presentations and publications as required by local/regional/national requirements.

13 Evaluation of patients for analysis

The analysis set will consist of the pregnancies among patients who are treated with basal insulin and have not changed basal insulin product 4 weeks prior to conception and during pregnancy.

14 Statistical considerations

Novo Nordisk A/S is responsible for the statistical analysis.

14.1 Sample size calculation

The sample size calculation is based on the combined primary endpoint, which is to compare the proportion of pregnancies in pregnant women treated with Levemir® to pregnant women treated with other basal insulin regimens which results in none of the 3 individual outcomes: major congenital malformations, perinatal and neonatal death.

Due to new knowledge obtained after study initiation regarding the observed split between treatment groups and pregnancy outcome incidence, a revised sample size calculation has been performed that takes the differences from the original assumptions into account. The original and revised sample size calculations are described in Sections 14.2 and 14.3, respectively.

14.2 Original sample size calculation

The following proportions are assumed for each of the individual outcomes as described in section 3.1:

- Major congenital malformations: 4.5%
- Perinatal death: 3%
- Neonatal death: 0.9%

The probability of the combination of the endpoints is not known in the literature but the proportion of pregnancies with any of the above outcomes will be estimated at 8.2% as described below. This combined probability is computed under the assumption that the individual outcomes are independent.

The primary endpoint is the proportion of pregnancies without any of the above outcomes. The proportions of patients not getting any of the outcomes is assumed to be:

- Major congenital malformations: 1 -0.045=0.955
- Perinatal death: 1-0.03=0.97
- Neonatal death: 1-0.009=0.991

None of the outcomes: 0.955 x 0.97 x 0.991 = 0.918, i.e. 91.8% of patients are expected not to get any of the pregnancy outcomes above, and 100%-91.8% = 8.2% are expected to get one of the outcomes.

The sample size calculation is based on the assumption that the proportion of pregnancies without the combined pregnancy outcome is 91.8% in the Levemir® group or the other basal insulin regimens group. The goal is to be able to detect a difference of 3.5% between the proportions without the combined endpoint in the Levemir® group compared to the other basal insulin regimens group. Assuming a maximum 1:2 split between the two groups, a sample size of 1,833 pregnancies is needed in order to have 80% power of achieving significance at 5% level (see Figure 14-1).

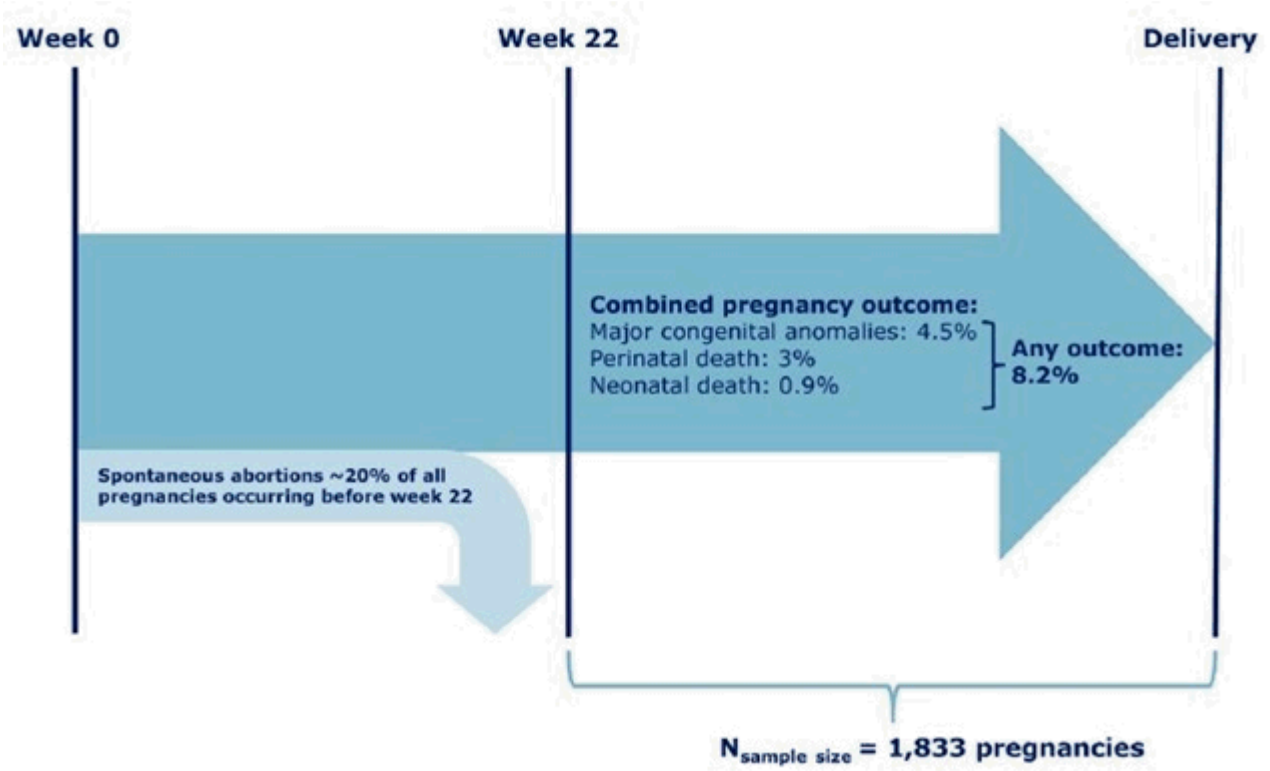

Figure 14-1 Sample size calculation

Thus, in total 1,833 pregnancies (including pregnancy outcome and follow-up in the infants) are needed assuming a maximum 1:2 balance between the two groups, (i.e. in the most extreme case there are 611 pregnancies in one group, and 1,222 pregnancies in the other group). With an estimated annual enrolment of 615 patients, this should be possible within the 5 years enrolment period as outlined in Section 6.1.

14.3 Revised sample size calculation

A revised sample size calculation has been performed based on a 1:1 split between the number of subjects treated with Levemir® and the number of subjects treated with other basal insulin products and a more realistic pregnancy outcome incidence, while keeping the other assumptions identical to those used in the original sample size calculation.

Figure 14-2 shows the revised sample size calculation based on a 1:1 split between the groups and pregnancy outcome incidences ranging from 92% to 96%. As indicated in the figure, a total sample size of 1222 (based on a 1:1 split including 611 subjects treated with Levemir® and 611 patients on other basal insulin regimens) will be sufficient to be able to detect a difference of 3.5% in the primary endpoint measure when the proportion of pregnancies resulting in none of the 3 pregnancy outcomes is ≥93.5%.

This sample size of 1222 is likely to be sufficient, even if the proportion of pregnancies resulting in none of the 3 pregnancy outcomes, unexpectedly, will be lower than the currently observed (97.3% observed versus 91.8% originally assumed).

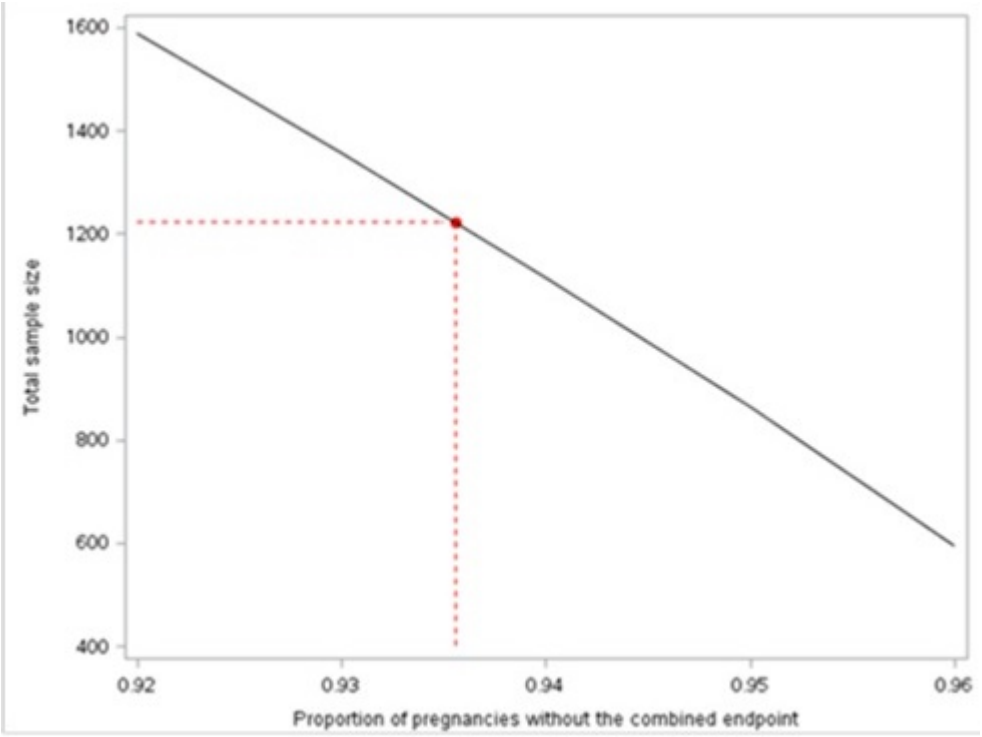

Figure 14-2 Total sample size sufficient to detect a minimal clinically relevant difference of 3.5% for proportion of pregnancies without the combined pregnancy outcome ranging from 92-96% (assuming a 1:1 split between the Levemir® group and the other basal insulin regimens group).

When calculating the number of subjects to be enrolled in the study, it has to be taken into account that not all subjects will be included from the primary analysis. The percentage of enrolled subjects, which are to be excluded from the primary analysis is approximately 40% and thereby in line with the original assumption used for the sample size calculation. Therefore, the sample size has been adjusted to 1222/ (1-0.40)=2037 (as a minimum) subjects to be enrolled in the study.

14.4 Statistical methods

All endpoints will be analysed on the analysis set.

Continuous variables (maternal HbA_{1c} at start of pregnancy, at the end of each trimester, and height and weight of the infant at 1 year) will be summarised with descriptive statistics (number of observations with available values, number of observations with missing values, mean, 95% confidence interval of the mean, standard deviation, minimum, median, maximum), and categorical variables and Apgar score will be displayed in frequency tables (N, %). The mean of the Apgar score will also be computed.

The primary endpoint, proportion of pregnancies resulting in the combined pregnancy outcome will be computed for the Levemir® group, and for the other basal insulin group, the difference between these proportions will be computed along with the 95% confidence interval and the p-value using Fisher's exact test. This simple analysis might be biased if type of basal insulin is confounded with other risk factors for a negative birth outcome, so to take this into account the primary endpoint will also be analysed using logistic regression, see the description below.

This analysis will be performed for all other endpoints which are proportions, both maternal endpoints, pregnancy outcome endpoints, and infants' endpoints at 1 year of age.

In addition, the primary endpoint will be analysed using logistic regression. Both crude and adjusted models will be performed. The model will include treatment group (Levemir®/other basal insulins group), and adjust for potential confounders such as study site, type of DM, race, hypertension, major hypoglycaemic events during pregnancy, folic acid intake, and use of GLP-1 agonists during pregnancy. Furthermore, HbA_{1c} at start of pregnancy, end of first trimester, and end of second trimester, age and BMI of the woman at baseline, duration of DM, blood pressure and previous foetal pregnancy complications will be adjusted for as appropriate. Adjustments will be performed in a stepwise manner, and further specified in the Statistical Analysis Plan. Similar analyses will be performed for all other endpoints which are proportions for maternal endpoints, or proportions for pregnancy outcome endpoints.

For the infants endpoints at 1 year of age the proportions will also be analysed using logistic regression, the model will include treatment group (Levemir®/other basal insulins group), study site, race, hypertension, major hypoglycaemic events during pregnancy, folic acid intake, and possible use of GLP-1 agonists during pregnancy as factors. Furthermore, HbA_{1c} at start of pregnancy, end of first trimester, and end of second trimester, age and BMI of the woman at baseline, duration of DM, blood pressure and previous foetal pregnancy complications will be included as covariates. The analyses regarding height and weight will also be adjusted for exclusive and/or partial lactation period.

The means of the continuous endpoints (maternal HbA_{1c} at the end of each trimester and, height and weight of the infant at 1 year), will be compared between the Levemir® group and the other basal insulins group using an analysis of covariance (ANCOVA) model.

The incidence of major hypoglycaemia during pregnancy will be computed for both treatment groups.

Additional exploratory hypothesis-generating analyses may also be performed as deemed relevant.

Differences in gestational age at study entry and exact follow-up time will be taken into account in the statistical analysis where relevant.

All statistical analyses will be performed using appropriate statistical software. All statistical tests will be performed as two-sided tests with a significance level of 0.05.

14.5 Interim analysis

No interim analysis is planned.

15 Ethics

The study will be conducted in accordance with Good Pharmacoepidemiology Practice (GPP) [19] and with the Declaration of Helsinki [20].

Patient data will be sent to the Diabetes Pregnancy Registry Database without any personal identifying data such as names and social security numbers. Patients will only be identifiable by their physician via the unique Diabetes Pregnancy Registry Patient ID and their date of birth. All data in the Diabetes Pregnancy Registry Database is anonymous.

15.1 Informed consent form for study patients

Informed consent from all study participants is required. In obtaining and documenting informed consent, the physician must comply with the applicable regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki [20].

Prior to any study-related activity, the physician must give the patient and/or the patient's legally acceptable representative (LAR) oral and written information about the study in a form that the patient or the patient's LAR can read and understand.

The requirement for using a patient's LAR is that the patient is unable to provide informed consent (e.g. is under age) and the process has been approved by the relevant IRB/IEC. If a patient is under age, then the patient's assent must also be obtained according to local requirements.

A voluntary, signed and personally dated, informed consent form will be obtained from the patient and/or the patient's LAR prior to any study-related activity.

The task of seeking informed consent can only be performed by the physician or another medically qualified person delegated by the physician, if permitted by local regulation, who must sign and date the patient information/informed consent form.

If information becomes available that may be relevant to the patient's willingness to continue participating in the study, the physician must inform the patient and/or the patient's LAR in a timely manner and a revised written informed consent must be obtained.

15.2 Data handling

If the patient (or the patient's LAR) withdraws the previously given informed consent the patient's data will be handled as follows:

- Data collected will be used as part of the study population

- ADRs and SAEs will be reported to Global Safety, Novo Nordisk A/S, regulatory authorities and to relevant Marketing Authorisation Holders by Novo Nordisk.

If data is used, it must always be in accordance with local law and IRB/IEC procedures.

15.3 Institutional Review Boards/Independent Ethics Committee

Before commencement of the study, the protocol, any amendments, patient information/informed consent form, any other written information to be provided to the patient, patient enrolment procedures, if any, the physician's current CV and/or other documentation evidencing qualifications, and other documents as required by the local IRB/IEC should be submitted. The submission letter should clearly identify (by study identification number, including version, title and/or date of the document) which documents have been submitted to the IRB/IEC. Written approval/favourable opinion must be obtained from IRB/IEC or other appropriate body as required locally before commencement of the study.

During the study, the physician must promptly in accordance with local requirements report the following to the IRB/IEC: unexpected serious ADRs, amendments to the protocol according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the patients, new information that may affect adversely the safety of the patients or the conduct of the study (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the patients), annually written summaries of the study status and other documents as required by the local IRB/IEC.

Amendments must not be implemented before approval/favourable opinion, unless necessary to eliminate immediate hazards to the patients.

The physician must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records should be filed in the physician's study file and copies must be sent to Novo Nordisk A/S.

15.4 Regulatory authorities

Regulatory authorities will receive the non-interventional study amendments to the protocol, reports on serious ADRs related to Novo Nordisk study products, and the non-interventional study report according to European and national requirements.

16 Premature termination of the study

The sponsor or a pertinent regulatory authority may decide to stop the study or part of the study at any time, but agreement on procedures to be followed must be obtained. An unplanned termination of the study could occur if any serious safety issue arise with the use of Levemir ® in the pregnant women assessed from the annual study reports.

If a study is prematurely terminated or suspended, the physician and/or sponsor should promptly inform the IEC/IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If after the termination of the study the risk/benefit analysis has changed, the new evaluation should be provided to the IEC/IRB in case it will have an impact on the planned follow-up of the patients who have participated in the study. If so, the actions needed to protect the patients should be described.

17 Critical documents

Before the physician starts the study (i.e. obtains informed consent from the first patient), the following documents must be available to Novo Nordisk A/S:

- Regulatory approval and/or notification as required
- CV of physician (current, dated and signed and/or supported by an official regulatory document)
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any amendment(s), if applicable
- Approval/favourable opinion from IRB/IEC or other appropriate body as required locally clearly identifying the documents reviewed: the protocol, any amendments, patient information/informed consent form and any other written information to be provided to the patient, patient enrolment procedures
- Copy of IRB/IEC approved patient information/informed consent form/any other written information/advertisement (or document of waiver by IRB/IEC of informed consent)
- Financial contract and study agreement document(s)

18 Responsibilities

The physician is accountable for the conduct of the study. If any tasks are delegated, the physician should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties.

The medical care given to, and medical decisions made on behalf of, patients should always be the responsibility of a qualified physician.

The physician must follow the instructions from Novo Nordisk A/S when processing data.

The physician must take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The physician must prevent any unauthorised access to data or any other processing of data against applicable law.

Upon request from Novo Nordisk A/S, the physician must provide the necessary information to enable Novo Nordisk A/S to ensure that such technical and organisational safety measures have been taken.

19 Reports and publications

The information obtained during the conduct of this study is considered confidential and can be used by Novo Nordisk A/S for regulatory purposes and for the safety surveillance of the study product. All information supplied by Novo Nordisk A/S in connection with this study must remain the sole property of Novo Nordisk A/S and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Novo Nordisk A/S. Such information must not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other studies with Levemir®, if deemed necessary by Novo Nordisk A/S.

An annual report of the study progress will be provided to EMA.

19.1 Communication and publication

Novo Nordisk A/S commits to communicating or otherwise making available for public disclosure results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or by other means.

Novo Nordisk A/S reserves the right not to release data until specified milestones, (e.g. a non-interventional study report is available). This includes the right not to release interim results from non-interventional studies, because such results may lead to conclusions that are later shown to be incorrect.

During and at the end of the study, one or more manuscripts for publication will be prepared. Novo Nordisk A/S will not suppress or veto publications; however Novo Nordisk A/S reserves the right to postpone publication and/or communication for a short time to protect intellectual property. The results of this study will be subject to public disclosure on external web sites according to international regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

19.1.1 Authorship

Authorship of publications should be in accordance with guidelines from The International Committee of Medical Journal Editors' Uniform Requirements (sometimes referred to as the Vancouver Criteria) [21].

19.1.2 Publications

The physician must ensure submission of the results of the study (either abstract or full study report) to IEC / IRB (or other appropriate bodies as required locally) if the protocol or protocol abstract was submitted to any of these.

In accordance with the commitment of Novo Nordisk A/S to be transparent on clinical trial activities this study will be registered by Novo Nordisk A/S at www.clinicaltrials.gov and www.novonordisk-trials.com in accordance with Novo Nordisk Clinical Trials Disclosure Code of Conduct.

In all cases, the study results must be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the study. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, the opinions of both the physicians and Novo Nordisk A/S must be fairly and sufficiently represented in the publication.

19.1.3 Site-specific publication(s)

At the end of the study, one or more public disclosures may be prepared collaboratively by the investigator(s) and Novo Nordisk A/S. Novo Nordisk A/S reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

For a multi-centre study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or patients, and therefore may not be supported by Novo Nordisk A/S. It is a policy of Novo Nordisk A/S that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the study.

In a multi-centre study based on the collaboration of all study sites, any publication of results in a journal article must acknowledge all study sites. Where required by the journal, the physician from each site will be named in the acknowledgement.

Novo Nordisk A/S maintains the right to be informed of any physician plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk study manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication. For PASS studies in Europe, an advance agreement on publication policy between Novo Nordisk and physician allows the latter to independently prepare publications based on the study results. Also PASS studies in Europe require Novo Nordisk A/S to communicate to the EMA and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication. This is to allow national competent authorities to review in advance the results and interpretations to be published.

19.2 Physician access to data and review of results

As owners of the study database, Novo Nordisk A/S has discretion over who will have access to the database. Generally, study databases are only made available to regulatory authorities.

Individual participating physician(s) will have their own research participants' data.

Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this study to researchers who require access for research projects studying the same disease and/or product studied in this study.

20 Retention of study documentation

Patient notes must be kept for the maximum period permitted by the hospital, institution or private practice.

Novo Nordisk A/S will comply with all the requirements of GPP related to archiving of study documentation and relevant national legislation related to archiving of study documentation. Records containing patient sensitive data must not be archived by Novo Nordisk A/S, but must be kept with the physician and patient and according to local regulations pertaining to personal data protection.

The physician must agree to archive the documentation pertaining to the study in an archive for at least 5 years after final report/first publication of the study, whichever comes later. The physician should not destroy any documents without prior permission from Novo Nordisk A/S.

Novo Nordisk A/S will retain the documentation pertaining to the study according to company procedure or in accordance with national regulations if they require a longer retention period.

21 Indemnity statement

Novo Nordisk A/S carries product liability for its products and liability assumed under the special laws, acts and/or guidelines for conducting non-interventional studies in any country, unless others have shown negligence.

Novo Nordisk A/S assumes no liability in the event of negligence or any other liability by the clinics or physicians conducting experiments or by persons for whom the said clinic or doctors are responsible.

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