PASS Progress Report no. 2

Study ID: NN304-4016

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

01 Nov 2014– 31 Oct 2015

Table of contents

Page

Table of figures

Page

Table of tables

Page

List of abbreviations

ADR	adverse drug reaction
DM	diabetes mellitus
EMA	European Medicines Agency
SAE	serious adverse event

1 Introduction

1.1 Background

Following the positive opinion from the European Medicines Agency (EMA) regarding the application for insulin detemir (Levemir®) use in pregnancy (EMEA/H/C/528/II/52), Novo Nordisk A/S committed to monitor the long-term safety of Levemir® during gestation and lactation, by establishing a registry for pregnant female patients with diabetes mellitus (DM). In accordance with the post-authorisation commitment to the EMA, a progress report on the status of patient enrolment of the registry will be submitted to the EMA on an annual basis.

This progress report provides an overview of the enrolment status for the Diabetes Pregnancy Registry between 01 Nov 2014 and 31 Oct 2015; the reporting period for the present report.

1.2 Diabetes Pregnancy Registry

1.2.1 Summary

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 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 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 within 4 weeks prior to conception and until delivery/pregnancy termination.

1.2.2 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

1.2.3 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.

1.2.4 Study design

This international, prospective, non-interventional, multicentre 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 fixed recruitment period of 5 years.

1.2.5 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) within 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.

1.2.6 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.

1.2.7 Exclusion criteria

Women who have been pregnant for more than 12 weeks at baseline visit will be excluded from the study.

1.2.8 Withdrawal criteria

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

1.2.9 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.

1.2.10 Study product(s)

Levemir® and other injectable antidiabetic treatment regimens.

2 Study progress

2.1 Study schedule

The planned number of patients to be included during the 5 years of recruitment period is 3,075.

The current planned dates for study completion and the final study report are listed below. Please note that planned timelines may be adjusted during the course of the study:

- Planned completion of the last patient last visit (LPLV): Q4 2019
- Planned final study report: Q1 2021

2.2 Enrolling countries

A total 409 patients have been enrolled in the Diabetes Pregnancy Registry in the reporting period 01 Nov 2014 - 31 Oct 2015 (for details, see Table 2-1). The planned distribution of patients by country is subject to variability and therefore might deviate from the planned number of patients presented in the protocol. The majority of the patients have been enrolled in Denmark, the United Kingdom and Croatia.

Table 2-1 Total enrolment stratified by country

Participating countries[a]	Number of patients enrolled		Completed[b]	Withdrawn
	Reporting Period	Total		
Croatia	70	145	29	1
Denmark	116	258	55	8
Finland	10	10	0	0
France	35	35	0	2
Israel	42	99	13	2
Netherlands	4	4	0	0
Poland	15	44	4	0
Spain	28	36	3	0
United kingdom	89	137	12	3
Total	**409**	**768**	**116**	**16**

a. Germany, Ireland, Romania, Italy and Norway have not enrolled any patients as of the cut-off date of this report.

b. Completed refers to: 1. abortion (spontaneous or induced) gestational week (GW) < 22; 2), neonatal death/perinatal death GW > 22; 3), live born infant and 1 year follow up (irrespective of whether there is a malformation or not).

2.3 Study Progress

Actual enrolment for the reporting period is approximately 68% of the planned enrolment (see Figure 2-1).

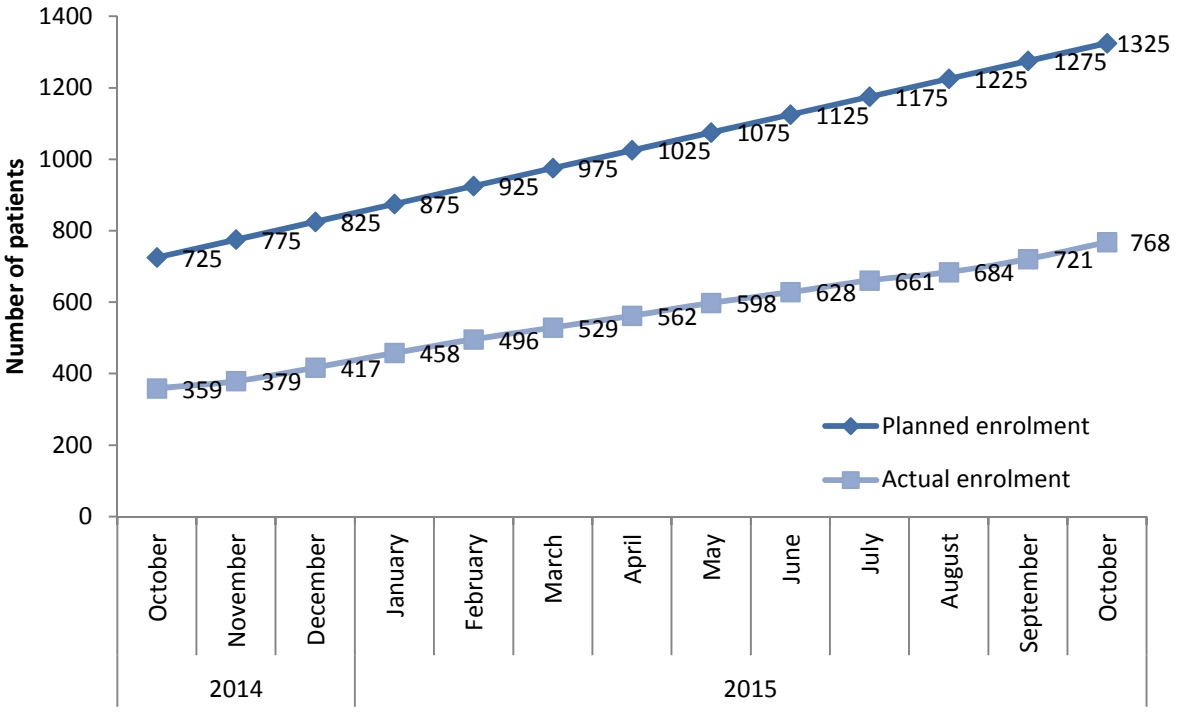

Figure 2-1 Actual versus planned enrolment in the reporting period 01 Nov 2014 – 31 Oct 2015

2.4 Actions taken during the reporting period

The following actions have been taken in the reporting period to improve recruitment rate:

1. The study protocol was amended to make the study easier to conduct. The following changes were made to the protocol:
    - Safety information was limited to systematic collection of ADRs and SAEs, as well as pre-eclampsia and major hypoglycaemic events
    - Concomitant medication will be recorded at baseline and during the first trimester
    - Current insulin/antidiabetic treatment and/or oral antidiabetic drug (OAD) will be reported at base line and in case of change in the type of product

2. Clinical sites in seven (7) additional countries have been included in the study – two (2) countries have already started enrolling patients (Table 2-1). The remaining 5 countries

are expected to have planned first patient first visit (FPFV) within the upcoming 6 months, depending on authority approval timelines.