PASS Progress Report No. 03

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 November 2015 – 31 October 2016

Title page

Study ID	NN304-4016 NIS (non-interventional study) and PASS (Post-Authorisation Safety Study)
ClinicalTrials.gov identifier	UTN No: U111-1132-9442
EU PAS register number	ENCEPP/SDPP/4137
EU PAS register link	http://www.encepp.eu/encepp/viewResource.htm?id=16553
Study initiated	Actual first patient first visit (FPFV): 30 Sep 2013
Sponsor	Novo Nordisk A/S Novo Allé 1, 2880 Bagsværd, Danmark
Data cut-off dates	01 November 2015 - 31 October 2016

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1 Background

This third progress report has been prepared in agreement with Post authorisation measure (PAM) 45 for Levemir®)

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 a progress report on the status of patient enrolment of the registry submitted to EMA annually.

This progress report provides an overview of the enrolment status for the Diabetes Pregnancy Registry between 01 November 2015 and 31 October 2016; the reporting period for the present report.

The cut-off for the data presented in the report is 01 November 2015 to 31 October 2016.

1.1 Diabetes Pregnancy Registry

1.1.1 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 anti-diabetic treatment regimens and their infants until 1 year of age.

A change in type or brand 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.

1.1.2 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.

1.1.3 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.

1.1.4 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 planned enrolment period of 5 years.

1.1.5 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 anti-diabetic 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 insulin's.

1.1.6 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 anti-diabetic treatment(s)
5. Unchanged basal insulin or other injectable anti-diabetic treatment product (for those not treated with basal insulin) 4 weeks prior to and following conception.

1.1.7 Exclusion criteria

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

1.1.8 Withdrawal criteria

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

1.1.9 Assessments

All adverse drug reactions (ADRs) and serious adverse events (SAEs) in pregnant women treated with any injectable anti-diabetic 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.

1.1.10 Study product(s)

Levemir® and other injectable anti-diabetic treatment regimens

2 Study progress

The planned number of patients to be included during the 5 years of recruitment period is 3,055.

The current planned dates for study completion and the final study report are listed below in Section 2.1.

2.1 Study Schedule

- Planned completion of the last patient last visit (LPLV): Q3 2020
- Planned final study report: Q1 2021

2.2 Enrolling countries

A total 626 patients have been enrolled in the Diabetes Pregnancy Registry in the reporting period 01 November 2015 - 31 October 2016 (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 Croatia, Denmark, Finland, Israel, Spain, and the United Kingdom.

Malaysia has been added as a new country and is expected to have first patient first visit (FPFV) by Q1 2017.

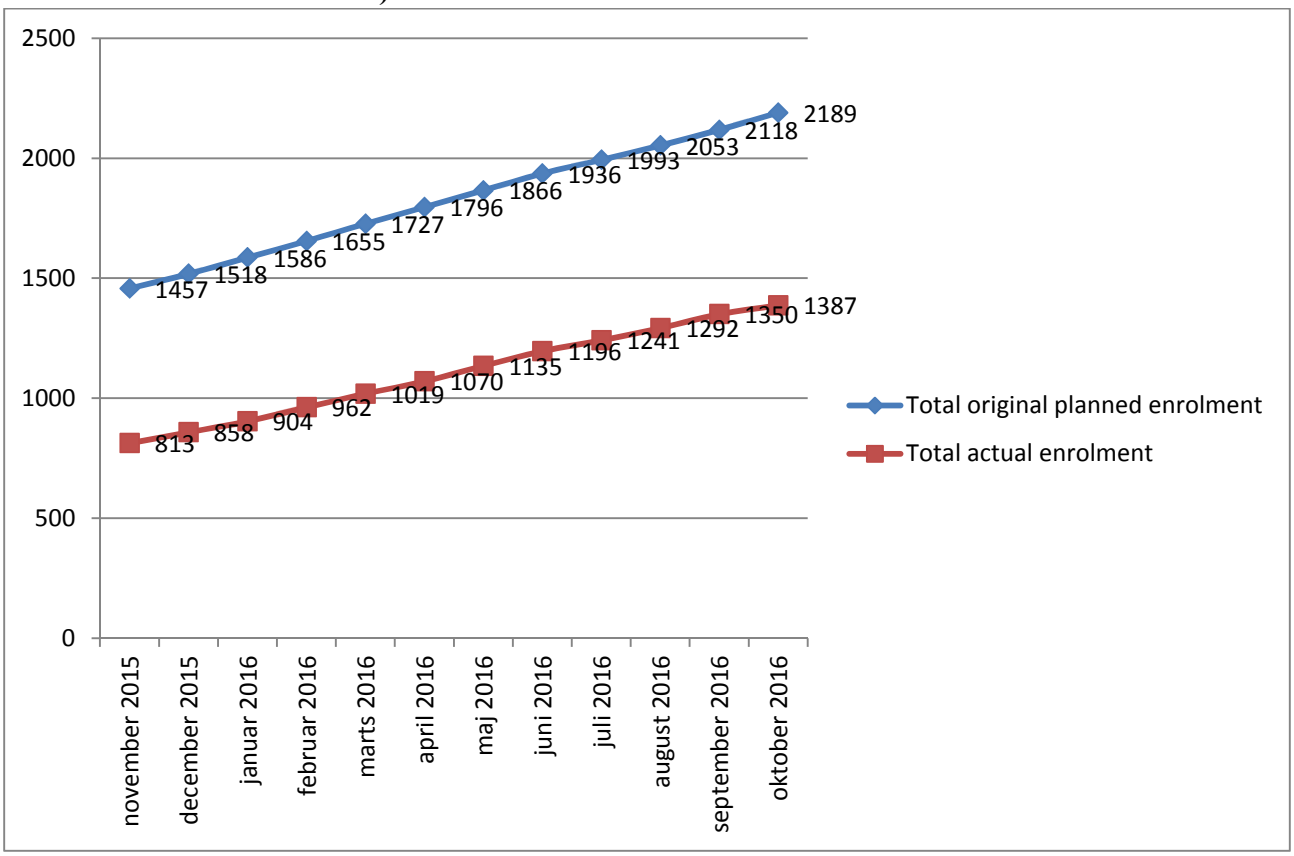
2.3 Study Progress

A total of 14 countries have enrolled patients into the study in the reporting period (13 countries from Europa and one, Israel, from the region International Operations) see Table 2–1 below.

Table 2–1 Number of patients enrolled and completed

Country	Enrolled - Reporting period (01 November 2015 - 31 October 2016)	Enrolled total in the period (30 Sep 2013 -31 Oct 2016)		
		Enrolled - Total	Completed	Withdrawn
Croatia	65	211	117	3
Denmark	161	420	190	21
Finland	60	70	4	0
France	49	84	5	3
Germany	10	10	0	1
Ireland	29	29	1	0
Israel	51	150	52	5
Italy	12	12	1	1
Netherlands	25	30	4	0
Norway	15	15	4	0
Poland	25	70	32	2
Romania	10	10	0	0
Spain	64	105	6	1
UK	50	171	56	14
Total	**626**	**1387**	**472**	**56**

Figure 2-1 Actual versus planned enrolment during the review period (01 November 2015 to 31 October 2016).



2.4 Actions taken during the reporting period

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

1. The study protocol was amended (Protocol Amendment No. 4, dated 11 February 2016) to increase enrolment. The following changes were made to the protocol:

   - The exclusion criterion has been changed from 12 to 16 weeks of pregnancy in order to facilitate enrolment.
   - 2 visit windows were implemented: one month to the 1 month follow-up visit (+1 month) and 4 months to the 1 year follow-up (+4 months) in order to increase convenience for patients and site staff.
   - The total number of women to be included in the study was corrected from 3,075 to 3,055 as the 3,075 originally stated in the protocol was a typo.

It is expected that all countries will have implemented this fourth amendment by end of the year 2016.

2. A country re-allocation was performed (28 July 2016) and here Malaysia was added as a new country in order to increase the total enrolment rate. It is expected that Malaysia will have the FPFV by end of December 2016 and they plan in total to enrol 75 patients to the study.

3. Additional sites have been added within the current participating countries.

2.5 Status

As illustrated in the Figure 2-1, the actual number of enrolled patients in the time period from 01 November 2015 to 31 October 2016 is lower than the planned number, however, we have seen an increase in the enrolment rate. The listed actions in Section 2.4 have been taken in order to further increase the enrolment of patients.

The final effect of the latest amendment and inclusion of additional sites and one country still remains.