PASS Progress Report No. 04

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 2016 – 31 October 2017

Title page

Study ID	NN304-4016 NIS (Non-Interventional Study) and PASS (Post-Authorisation Safety Study)
ClinicalTrials.gov identifier	UTN No: U1111-1132-9442
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, DK-2880 Bagsværd, Danmark
Data cut-off dates	01 November 2016 - 31 October 2017

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1 Background

This fourth 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 is submitted to EMA annually.

This progress report provides an overview of the enrolment status for the Diabetes Pregnancy Registry between 01 November 2016 and 31 October 2017; the reporting period for the present report.

The cut-off for the data presented in the report is 01 November 2016 to 31 October 2017.

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 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 of basal insulin after baseline visit will lead to exclusion from the primary and secondary endpoint analyses, 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 are treated with Levemir® to pregnant women who have completed 22 weeks of pregnancy and are 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 analysis, 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, preeclampsia 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

According to the Protocol (version 4.0, dated 12 Feb 2016) the planned number of patients to be included during the 5 years of estimated recruitment period is 3,055.

2.1 Study Schedule

According to the Protocol (version 4.0, dated 12 Feb 2016):

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

2.2 Enrolling countries

A total of 828 patients have been enrolled in the Diabetes Pregnancy Registry in the reporting period 01 November 2016 – 31 October 2017 (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, Israel, Spain and the United Kingdom.

We have added three new countries to enrol patients into the study:

1. Malaysia had the first patient first visit (FPFV) 02 March 2017
2. Greece had the FPFV 03 August 2017
3. Portugal had the FPFV 02 October 2017

2.3 Study Progress

A total of 17 countries have enrolled patients into the study in the reporting period (15 countries from Europa and two outside of Europe, i.e. Israel and Malaysia, see Table 2–1 below).

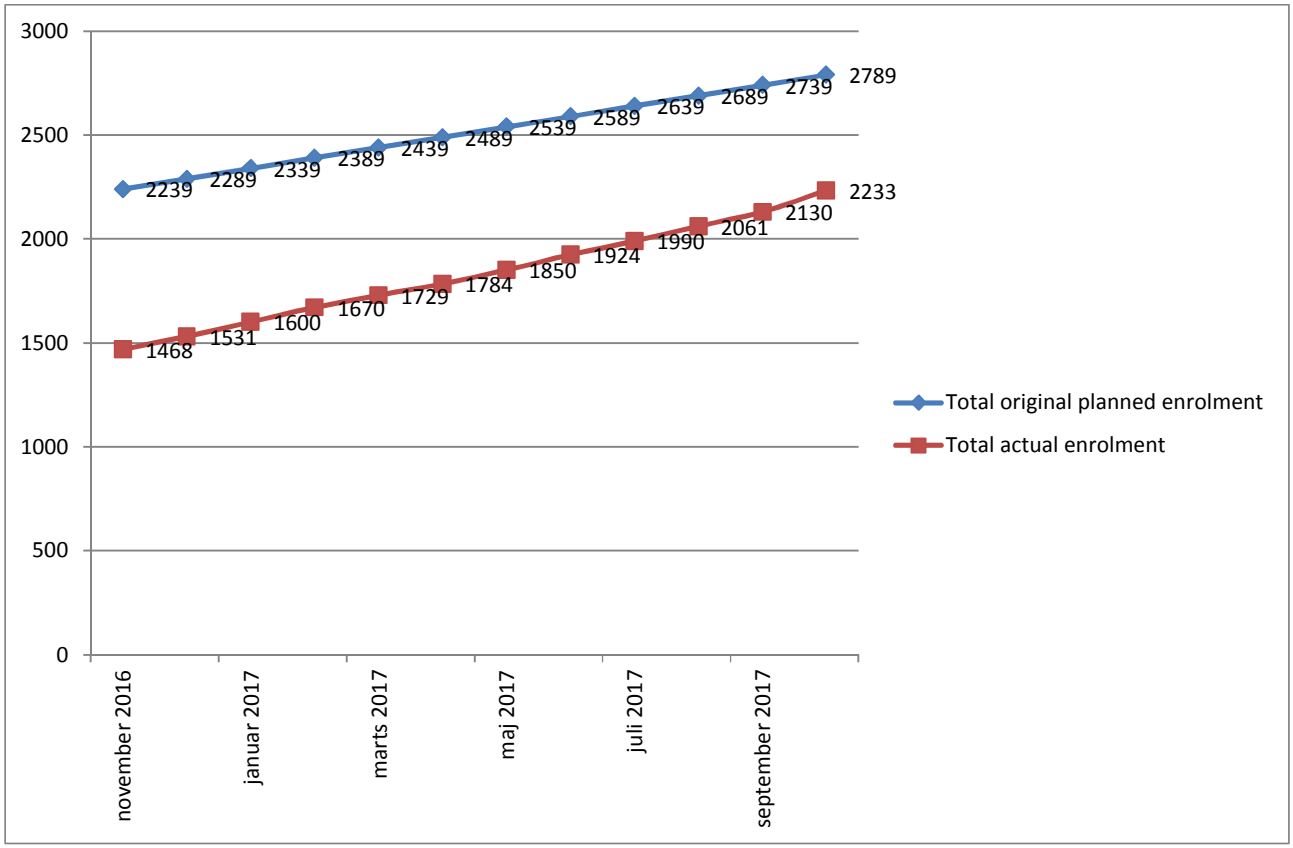
Table 2–1 Number of patients enrolled and completed

Country	Enrolled - Reporting period (01 November 2016- 31 October 2017)	Enrolled total in the period (30 Sep 2013 -31 Oct 2017)		
		Enrolled - Total	Completed[a]	Withdrawn and Lost to follow-up
Croatia	85	296	180	6
Denmark	162	588	313	29
Finland	68	140	40	1
France	48	138	40	5
Germany	20	30	4	3
Greece	7	7	0	0
Ireland	35	65	7	2
Israel	54	204	101	8
Italy	39	52	2	2
Malaysia	21	21	2	0
Netherlands	32	62	14	0
Norway	27	42	7	0
Poland	40	112	53	2
Portugal	5	5	0	0
Romania	12	23	3	0
Spain	54	158	72	1
UK	119	290	86	26
Total	**828**	**2233[b]**	**924**	**85**

[a]:A completer is per protocol defined as: abortion, perinatal death, neonatal death or completion of 1 month and 1 year follow-up data collection of the infant(s).

[b]: A total of 18 patients were enrolled in the previous report period but were not included in the previous NN304-4016 progress report (23 Dec 2016) due to late registration in the Novo Nordisk systems. These 18 patients have been included in the total number of patients in this table.

Figure 2-1 Actual versus planned enrolment during the review period (01 November 2016 to 31 October 2017)



2.4 Actions taken during the reporting period

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

1. The study protocol was amended (Protocol Amendment No. 04, dated 11 February 2016), where the exclusion criterion was changed to exclude woman who have been pregnant for more than 16 weeks at baseline visit (previously defined as 12 weeks). An increased enrolment rate has been observed for several sites following the amendment.

2. A country re-allocation was performed in March 2017, where Greece and Portugal were added as new countries in order to increase the total enrolment rate.

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

4. A protocol amendment (Protocol Amendment No.06, dated 07 September 2017) was submitted to PRAC/EMA on the 15 September 2017. The rationale behind the amendment is that the distribution of patients' treatment split Levemir® vs. other basal insulin regimens is approximately 1:1, whereas the original sample size calculation was based on the assumption of a 1:2 split between the two groups. Furthermore we have seen that the observed number of events for the primary endpoint (major congenital malformations, peri- and neonatal death) is lower than originally anticipated. Based on these findings, we have suggested amending the protocol in order to reduce the total sample size without compromising the objective of the study.

2.5 Status

As depicted in the Figure 2-1, the actual number of enrolled patients in the time period from 01 November 2016 to 31 October 2017 is higher than the planned number (planned number 550, enrolled number 765).
However, the actual number of enrolled subjects as of 31 October 2017 is lower than originally planned. The listed actions in Section 2.4 have been taken in order to further increase the enrolment rate of patients.