PASS Progress Report No. 05

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 2017 to 31 October 2018

Title page

Study ID	NN304-4016 NIS (non-interventional study) PASS (post-authorisation-safety-study)
ClinicalTrials.gov identifier	NCT: 01892319
EU PAS register number	ENCEPP/SDPP/4137 (EUPAS4137)
EU PAS register link	http://www.encepp.eu/encepp/viewResource.htm?id=25527
Study initiated	Date of the first patient first visit: 30-Sep-2013
Sponsor	Novo Nordisk A/S Novo Allé 1, DK-2880 Bagsværd Denmark
Data cut-off dates	Reporting period: From 01 November 2017 to 31 October 2018.

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1 Background

This fifth progress report has been prepared in agreement with Post Authorisation Measure (PAM) 45 (MEA 045) 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 2017 and 31 October 2018; the reporting period for the present report.

As the enrolment was completed by end of December 2017 (last patient first visit (LPFV) on 29 December 2017) the report will also include the entire enrolment period starting from first patient first visit (FPFV) on 30 September 2013.

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 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 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 the 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 preeclampsia 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 monitors and assesses the safety of Levemir® use during pregnancy as well as monitors the health status of the infants at 1 month and 1 year of age. The same parameters will 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 had a planned enrolment period of 5 years. The last patient was included on 29 December 2017 and hereby the enrolment period has been completed.

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 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 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 insulins.

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 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.

1.1.7 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 antidiabetic treatment regimens, as well as in their offspring 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 antidiabetic treatment regimens.

2 Study progress

In total 3 global protocol amendments have been generated:

- Global protocol amendment no. 01, dated 05 December 2014.
- Global protocol amendment no. 04, dated 11 February 2016.
- Global protocol amendment no. 06, dated 07 September 2017.

The last global amendment no. 06, proposed a reduction in the overall sample size as the observed distribution of patients treated with Levemir® vs. other basal insulin regimens, was approximately 1:1, whereas the original sample size calculation was based on the assumption of a 1:2 treatment split between the 2 groups. Hereby the overall sample size was reduced from 3055 to 2037 striving for that 611 patients treated with Levemir® will be eligible for the primary analysis.

Eligible for the primary analysis is defined as the patients treated with Levemir® or other injectable basal insulin regimens, which have not changed the basal insulin product 4 weeks prior to conception and until delivery/pregnancy termination.

With an anticipated drop-out rate of 40% of non-eligible patients, this corresponds to a demand for 1222 patients with eligible pregnancy outcomes.

After the approval of global amendment no. 06, it was decided to close the enrolment and on 29 December 2017, the last patient number 2446, was enrolled.

2.1 Study Schedule

- Planned completion of the LPLV: Q4 2019.
- Planned final study report: Q4 2020.

The study timelines have been updated compared to the 4th progress report as agreed with the Agency and in accordance with the latest protocol amendment (Protocol amendment No.06, dated 07 September 2017 and submitted to PRAC/EMA on 15 September 2017) where the total sample size was reduced to 2,037 patients. As more patients progress in the study, the study timelines may be further revised.

2.2 Enrolling countries

Initially the following countries were included in the study: Croatia, Denmark, France, Israel, Poland, Spain and UK. Over time the listed countries below have been added and have enrolled patients into the study:

- Finland had the FPFV on 21 September 2015.
- Netherland had the FPFV on 09 October 2015.
- Germany had the FPFV on 23 November 2015.

- Romania had the FPFV on 19 January 2016.
- Ireland had the FPFV on 10 February 2016.
- Italy had the FPFV on 04 March 2016.
- Norway had the FPFV on 14 March 2016.
- Malaysia had the FPFV on 02 March 2017.
- Greece had the FPFV on 03 August 2017.
- Portugal had the FPFV on 02 October 2017.

A total of 17 countries and 92 sites have enrolled patients into the study (15 countries from Europe and two outside of Europe, i.e. Israel and Malaysia).

2.3 Study Progress

A total of 213 patients have been enrolled into the study in the reporting period from 01 November 2017 to 31 October 2018 (for details, see Table 2-1).

In the total study period, from FPFV on 30 September 2013 to LPFV, a total of 2446 patients have been enrolled into the study. The LPFV was on 29 December 2017 and no more patients have been enrolled after this date.

As of 31 October 2018, a total of 671 patients are qualifying for the primary analysis and are treated with Levemir®. As the data still is preliminary, this number might change over time.

For the distribution of patients in the entire enrolment period as well as for the reporting period, please see Table 2-1 and for the enrolment over time (from FPFV to LPFV) please see the Figure 2-1.

Table 2-1 Number of patients enrolled, completed withdrawn or lost to follow-up:

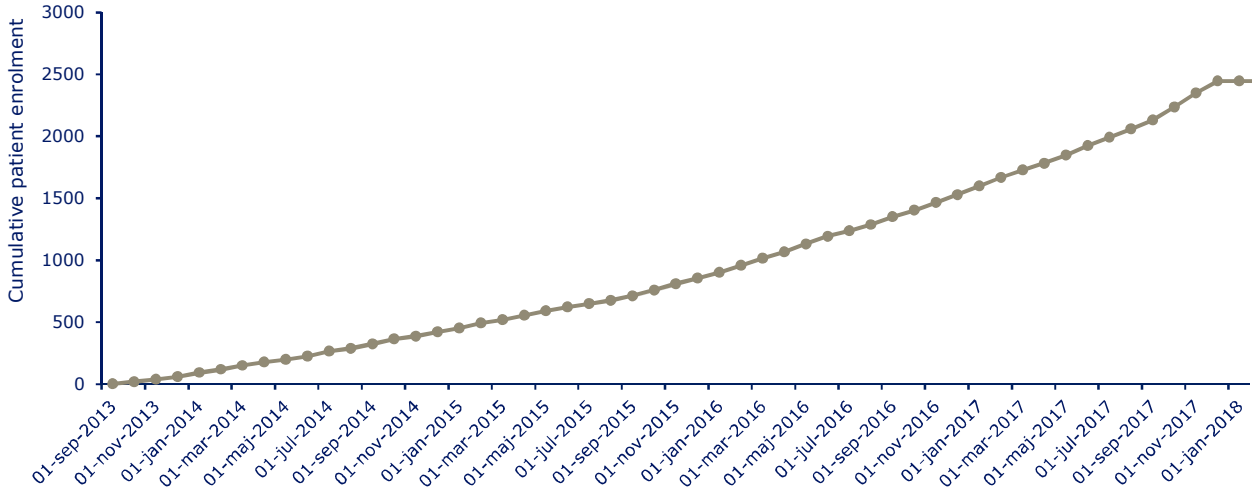
	Enrolled. Reporting period: 01 Nov 2017 to 31 Oct 2018	**Enrolled. Entire enrolment period: 30 Sep 2013 to 29 Dec 2017**	**Completed[a] by 31 Oct 2018**	**Withdrawn or lost to follow-up by 31 Oct 2018**
Croatia	15	311	238	4[b]
Denmark	39	627	458	21[b]
Finland	10	150	102	1
France	27	165	68	12
Germany	5	35	13	1[b]
Greece	4	11	1	0
Ireland	9	74	36	0[b]

	Enrolled. Reporting period: 01 Nov 2017 to 31 Oct 2018	Enrolled. Entire enrolment period: 30 Sep 2013 to 29 Dec 2017	Completed[a] by 31 Oct 2018	Withdrawn or lost to follow-up by 31 Oct 2018
Israel	11	215	117	9
Italy	18	70	24	3
Malaysia	6	27	4	0
Netherlands	8	70	44	0
Norway	3	45	20	1
Poland	15	127	87	2
Portugal	14	19	4	1
Romania	3	26	14	0
Spain	10	168	109	5
UK	16	306	152	33
Total	**213**	**2446**	**1491**	**93**

[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] Less patients are listed as withdrawn or lost to follow-up than in the previous progress reported. The numbers have been updated after monitoring and confirmation from the sites that some of the patients were not withdrawn or lost to follow-up.

Figure 2-1 Cumulative enrolment, from FPFV on 30 September 2013 to LPFV on 29 December 2017:



2.4 Actions taken during the reporting period

The global protocol amendment no.06 (see Section 2) was submitted to PRAC/EMA on 15 September 2017.

Novo Nordisk received the approval on 15 December 2017. Hereafter it was decided to stop the enrolment of patients into the study by end of the month, where the number of patients enrolled, exceeded the minimum necessary number of patients according to the calculation of sample size in the amendment.

2.5 Status

According to the global protocol amendment no.06, a minimum of 2037 patients were necessary to be enrolled into the study to secure enough patients for the primary analysis (see Section 2).

A total of 213 patients have been enrolled in the reporting period from 01 November 2017 to 31 October 2018.

A total of 2446 patients have been enrolled in the period from 30 September 2013 to 29 December 2017.

For more details on the enrolled patients, please see the Section 2.3