# PASS Progress Report

# Study ID: NN9535-4447

# Epidemiological assessment of the risk for pancreatic cancer associated with the use of Ozempic® (semaglutide s.c.) in patients with type 2 diabetes

## - A cohort study based on Nordic registry data

# Title page

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|---|---|
| **Study ID** | Study ID: NN9535-4447 |
| **ClinicalTrials.gov identifier** | NCT04572165 |
| **EU PAS register number** | EUPAS37258 |
| **EU PAS register link** | http://www.encepp.eu/encepp/viewResource.htm?id=37259 |
| **Study initiated** | Start of data collection is not initiated |
| **Sponsor** | Novo Nordisk A/S<br>Novo Allé<br>DK-2880 Bagsværd<br>Denmark |
| **Data cut-off date** | Data cut-off date for this progress report is December 31st, 2019 for Norway, Sweden, and Denmark |

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# 1 Background

This progress report no 1 of 4 has been prepared in agreement with the commitment as specified in the protocol. Reference is made to PASS Protocol NN9535-4447 - EMEA/H/C/004174/MEA/002 (Ozempic®, sequence 0011). The cut-off for the data presented in the report is December 31st, 2019.

The NN9535-4447 study is a post-authorisation safety study (PASS). The aim of this study is to evaluate whether exposure to Ozempic® increases the risk of pancreatic cancer in patients with type 2 diabetes. This is achieved by estimating the risk of pancreatic cancer associated with Ozempic® use as compared to use of other non-incretin antidiabetic drugs used at a similar stage as Ozempic® in the treatment cascade in the type 2 diabetes population.

The study is sponsored by Novo Nordisk A/S while Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark is the coordinating study entity.

# 2 Study progress

The purpose of the annual progress report for this study is to monitor the accumulation of patients exposed to Ozempic® to confirm assumptions about the study's statistical power, and to provide an update on the multinational collaboration.

The study progress report will be based on public aggregated data and the data cut-off is 31st December 2019 for Norway, Sweden, and Denmark. The focus of this report is mainly to document the progress in establishing the cross-country collaboration and application for data access as well as to monitor/estimate the accumulation of patients exposed to Ozempic® in the study databases.

## 2.1 Study Schedule

During EMA assessment of the oral semaglutide Marketing Authorisation Application in 2019, it was requested to amend the study protocol to include also new users of oral semaglutide (Rybelsus®). Due to such amendment of the study protocol (Ozempic® (EMEA/H/C/004174/MEA/PRO002, sequence 0054), Rybelsus® (EMEA/H/C/004953/MEA/002)) and consequent changed scope of the study, the early milestones of the study as specified in the original study protocol were postponed. Original and updated milestones are listed in the table below.

| **Milestone** | **Planned date original protocol** | **Planned date amended protocol** |
|---|---|---|
| First subject prescribed Ozempic® in Denmark, Sweden, and Norway | Q3 2018 (Denmark)<br>Q4 2018 (Sweden and Norway) | 2018 |
| Registration in the EU PAS Register<br>*Note: The study was registered in EU PAS in Q3 2020* | Q2 2020 | Q3 2020 |
| Application for data access and approvals in Denmark<br>*Note: Access to Danish data is in place Q4 2020* | Q2 2019 | Q2 2020 |
| Finalization of common Statistical Analysis Plan (SAP)<br>*Note: The SAP is expected to be finalized Q4 2020* | Q4 2019 | Q4 2020 |
| Start of data collection (Time of first data extraction in Denmark)<br>*Note: Data extraction will take place when the ENCePP seal is accepted. Data extraction is expected in Q4 2020 or Q1 2021* | Q2 2020 | Q4 2020 |
| Application for ethical approval in Norway and Sweden (not required in Denmark)<br>*Note: Expected to be finalized Q1 2021* | | Q4 2020 |
| Last subject prescribed Ozempic® to be included in the study | Q4 2022 | Q4 2022 |
| Application for data access in Norway | | Q4 2023 |
| Application for data access in Sweden | | Q1 2024 |
| End of data collection (Time of last data extraction) | Q3 2024 | Q4 2024 |
| Study progress report 1 | Q4 2020 | Q4 2020 |
| Study progress report 2 | Q4 2021 | Q3 2021 |
| Study progress report 3 | Q4 2022 | Q3 2022 |
| Study progress report 4 | Q4 2023 | Q3 2023 |
| Final report of study results | Q3 2025 | Q1 2026 |

## 2.2 Enrolling countries

**Table 1 Collaborating sites, part of the NN9535-4447 study collaboration**

| Country | Department, Institute | Abbreviation | Role |
|---|---|---|---|
| Denmark | Clinical Pharmacology and Pharmacy, University of Southern Denmark, Odense | SDU | Coordinating study entity |
| Sweden | Centre for Pharmacoepidemiology, Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm | KI | Collaborator |
| Norway | Norwegian Institute of Public Health, Department of Chronic Diseases and Ageing, Oslo | NIPH | Collaborator |

An agreement was completed between Novo Nordisk and University of Southern Denmark before the first version of the protocol was submitted to PRAC.

Subcontracts between SDU and research partners KI and NIPH are in the process of being prepared.

## 2.3 Study Progress

For the purpose of the progress report, data are extracted from publicly available databases in Norway, Sweden, and Denmark. These databases include information on number of individual Ozempic® users by sex and age. The data cut-off date is December 31st, 2019 as Denmark and Sweden only have data available for this period.

The number of patients exposed to Ozempic® fulfils the expectations specified in the protocol (Table 2).

**Table 2 Observed total number of unique patients exposed to Ozempic® as compared to estimated total Ozempic® exposure in the study protocol**

| | 2018 | 2019 |
|---|---|---|
| Person-years of Ozempic® exposure as estimated in the study protocol to inform power calculations<br>Total population (Denmark, Norway and Sweden) | 2,000 | 9,000 |
| Number of unique patients exposed to Ozempic® as observed in the databases<br>Total population (Denmark, Norway and Sweden) | 6,590 | 40,756 |

The estimated Ozempic® exposure presented in the study protocol are the projected person-years of treatment (assuming each patient is treated for a full year) and were based on sales forecasts/volume estimates. The numbers therefore reflect the hypothetical scenario where all patients initiating Ozempic® in a given year remain treated for a full year and it is for this reason a conservative estimate of the number of unique users of Ozempic® in that same year. This is also what can be observed from Table 2, where the observed level of Ozempic® use exceeds the estimate used to inform the power calculations. Of note, the observed number of unique users of Ozempic® will conversely be an overestimate of the number of person-years of follow-up for pancreatic cancer, as

not all users initiating Ozempic® within a given year will be available for a full year of follow-up. Nevertheless, the observed levels of Ozempic® exposure in 2018 and 2019 contribute a considerable number of patients with several years of potential follow-up before the study period ends in 2023.

**Table 3 Number of patients exposed to Ozempic® in available databases in countries included in the study**

| Country | Population covered by databases | Commercial launch dates for Ozempic® | Data coverage | Number of unique Ozempic® users | Stratified by age and sex |
|---|---|---|---|---|---|
| Denmark* | Nationwide, 5.7 million individuals | August 20th, 2018 | 2018 - 2019 | **2018:** 5,745** | Male: 3,320; Female: 2,430<br>18-24y: 20; 25-44y: 495;<br>45-64y: 2,845; 65-79y: 2,220; 80+y: 170 |
| | | | | **2019:** 21,905** | Male: 12,685; Female: 9,215<br>18-24y: 65; 25-44y: 1,940;<br>45-64y: 10,750; 65-79y: 8,315; 80+y: 830 |
| Norway | Nationwide, 5.2 million individuals | February 1st, 2019 | 2018 - 2019 | **2018:** 18 | Male: 6; Female: 12<br>(age-stratification not possible due to low counts) |
| | | | | **2019:** 5,252*** | Male: 2,912; Female: 2,340<br>20-24y: 33; 25-34y: 139;<br>35-44y: 445; 45-54y: 1,143; 55-64y: 1,631;<br>65-74y: 1,351; 75-84y: 451; 85-90y+: 59 |
| Sweden* | Nationwide, 10.1 million individuals | October 26th, 2018 | 2018 - 2019 | **2018:** 827*** | Male: 522; Female: 305<br>20-24y: 5; 25-34y: 15; 35-44y: 62; 45-54y: 152; 55-64y: 257; 65-74y: 252; 75-84y: 77; 85y+: 7 |
| | | | | **2019:** 13,599*** | Male: 7,968; Female: 5,631<br>20-24y: 52; 25-34y: 294; 35-44y: 829; 45-54y: 2,393; 55-64y: 4,080; 65-74y: 4,183; 75-84y: 1,627; 85y+: 141 |

* Unique users within the specific calendar year. Data on unique users across calendar years are currently not available. To achieve homogeneity, Norwegian data are listed in the same way.

**Small strata for age and sex are rounded why slight differences may appear in strata specific numbers and total numbers.

***Publicly available data from Norway and Sweden include age stratification by the age group 15-19 years. As prescriptions in patients below 18 years of age is outside the approved label of Ozempic® and due to the inclusion criteria in the study requiring age ≥18 years, use of Ozempic® in age groups under 20 years are not included in the progress report.

## Table 4 Status on data access in collaborating countries

| Countries | Status |
|---|---|
| Denmark | Application for data access in Denmark is accepted and data extraction will take place when the ENCePP seal is finally settled. Data extraction will include data on Ozempic® users from the Danish commercial launch date. |
| Norway | Application for the approvals for the full linked data (ethics approval and "unntak fra taushetsplikt" from the Regional Ethics Committee South-East, Data Protection Impact Assessment (DPIA) from NIPHs "personvernombud", data order to respective data holders) is in preparation. |
| Sweden | Applications for ethical approval from the Swedish Ethical Review Authority and data order from the National Board of Health and Welfare and Statistics Sweden is in preparation. |

## Table 5 Meetings

| Date | Participants | Purpose | Main agenda points |
|---|---|---|---|
| November 11th, 2019<br>Copenhagen | University of Southern Denmark (SDU)<br><br>Karolinska Institute (KI)<br><br>Norwegian Institute of Public Health (NIPH)<br><br>Novo Nordisk | Adjustment of the study protocol according to the PRAC assessment and to collect input from Norway and Sweden to the research methodology | ENCePP seal<br><br>Discussion of protocol<br>- Meta-analysis across national data. Due to legislative changes in data sharing between Denmark and Norway/Sweden it is no longer possible to pool individual-level data from all sites prior to statistical analysis.<br><br>Postponement of submission of final report to Q1 2026 and the possibility to include Swedish cancer data for 2022.<br><br>Statistical analysis plan (SAP), planning |
| **Date** | **Participants** | **Purpose** | **Main agenda points** |
| September 2nd, 2020<br><br>Virtual meeting | University of Southern Denmark (SDU)<br><br>Karolinska Institute (KI)<br><br>Norwegian Institute of Public Health (NIPH)<br><br>Novo Nordisk | SAP<br><br>Timelines | Planning and development of the SAP<br>- Classification of study variables<br><br>Discussion of propensity score methods |
| **Date** | **Participants** | **Purpose** | **Main agenda points** |
| November 5th, 2020<br>Virtual meeting | University of Southern Denmark (SDU)<br><br>Karolinska Institute (KI)<br><br>Norwegian Institute of Public Health (NIPH)<br><br>Novo Nordisk | SAP<br><br>Timelines | Development of the SAP<br>- Principal discussions<br>- "talk through" of the programmer's manual in relation to a common data model<br>- Follow-up from last meeting concerning variable definitions<br>- Propensity score<br>o Estimation |

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| | | | ○ Matching<br><br>Preparing the first study progress report |
| **Date** | **Participants** | **Purpose** | **Main agenda points** |
| December 10th, 2020<br><br>Virtual meeting | University of Southern Denmark (SDU)<br><br>Karolinska Institute (KI)<br><br>Norwegian Institute of Public Health (NIPH)<br><br>Novo Nordisk | SAP<br><br>Status | Development of the SAP<br>- "talk through" of the programmer's manual in relation to a common data model<br>Status<br>- Progress report preparation<br>- ENCePP seal application<br>- Research agreements<br>- Protocol amendment, re-submission |

## 2.4 Status

The NN9535-4447 study is progressing as planned in terms of product utilisation, EU PAS registration, application for data access, and the research collaboration. An amendment of the study protocol for Ozempic® (EMEA/H/C/004174/MEA/PRO 002, sequence 0054), and Rybelsus® (EMEA/H/C/004953/MEA/002) was submitted to PRAC July 16th, 2020. A PRAC assessment was received November 16th, 2020 with a request that entailed a new protocol amendment to be resubmitted within 60 days. An amendment was subsequently submitted on December 4th, 2020 for both Ozempic® (EMEA/H/C/004174/MEA/002.1, sequence 0064) and Rybelsus® (EMEA/H/C/004953/MEA/002).

The number of patients exposed to Ozempic® in 2018 and 2019 fulfils the expectations specified in the protocol. The large uptake of Ozempic® in the early years after launch is of importance as it contributes a considerable number of patients with several years of follow-up for pancreatic cancer in the study.

The Marketing Authorisation Holder (MAH) Novo Nordisk A/S submitted the EU PAS registration on September 30th, 2020.

The SDU entity submitted the ENCePP seal on October 9th, 2020 and is awaiting approval. Application for data access in Denmark is accepted and data extraction will take place when the ENCePP seal is finally settled.

The research collaboration is well established and is progressing in terms of development of the statistical analysis plan and common data model.