PASS Progress Report

Study ID: NN9535-4447

Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with type 2 diabetes
- A cohort study based on Nordic registry data

Title page

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	Actual start of data collection (time of first data extraction in Denmark): *26 January 2021*
Sponsor	Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark
Data cut-off date	*31 December 2020* is the data cut-off date for this progress report for Norway, Sweden, and Denmark

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1 Background

This progress report no 2 of 4 has been prepared in agreement with the commitment as specified in the protocol. Reference is made to PASS Protocol NN9535-4447 - (Ozempic®, sequence 0064) and (Rybelsus®, sequence 0023).

The cut-off for the data presented in the report is 31 December 2020.

The NN9535-4447 study is a post-authorisation safety study (PASS). Since submission of progress report 1, an amended study protocol for Ozempic®, sequence 0064 and Rybelsus®, sequence 0023 has been approved by PRAC and the overall scope of the study was changed to include both Ozempic® and Rybelsus®. The aim of this study is to evaluate whether exposure to semaglutide influences the risk of pancreatic cancer in patients with type 2 diabetes. This is achieved by estimating the risk of pancreatic cancer associated with semaglutide use as compared to use of other non-incretin antidiabetic drugs used at a similar stage as Ozempic® or Rybelsus® in the treatment of type 2 diabetes.

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 and the collaborating sites are Centre for Pharmacoepidemiology, Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm and the Norwegian Institute of Public Health, Department of Chronic Diseases and Ageing, Oslo.

2 Study progress

The purpose of the annual progress report for this study is to monitor the accumulation of patients exposed to semaglutide (Ozempic® and Rybelsus®) in the study databases to confirm assumptions about the study's statistical power, and to provide an update on the multinational collaboration including data access.

The study progress report is based on publicly available aggregated data and the data cut-off is 31 December 2020 for Norway, Sweden, and Denmark.

2.1 Study Schedule

- Planned end of data collection (time of last data extraction): Q4 2024
- Planned final study report: Q1 2026

The planned timelines may be adjusted during the course of the study. According to the milestones specified in the study protocol, the Statistical Analysis Plan (SAP) was planned to be finalized in Q4 2020. However, due to the amendment of the study protocol the finalization of the SAP will be postponed to Q4 2021.

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

The agreement between Novo Nordisk and University of Southern Denmark is in place. 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 semaglutide users by sex and age. The data cut-off date is 31 December 2020.

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

Table 2 Actual total number of unique patients exposed to semaglutide (Ozempic® and Rybelsus®) as compared to planned/estimated total semaglutide exposure in the study protocol

	2018	2019	2020
Planned person-years of semaglutide exposure as estimated in the study protocol to inform power calculations Total population (Denmark, Norway and Sweden)	2,000	24,000	52,000
Actual number of unique patients exposed to semaglutide as observed in the databases Total population (Denmark, Norway and Sweden)	6,592	40,751	84,950

The estimated semaglutide exposure presented in the study protocol consists of the projected person-years of treatment (assuming each patient is treated for a full year) and was based on sales forecasts/volume estimates. The numbers therefore reflect the hypothetical scenario where all patients initiating semaglutide in a given year remain treated for a full year. It is for this reason therefore a conservative estimate of the number of unique users of semaglutide in that same year as not all patients will be using semaglutide for a full year. This is also what can be observed from Table 2, where the number of unique users of semaglutide are higher than the projected person-years of treatment that has been used to inform the power calculations. Of note, the observed number of unique users of semaglutide will conversely be an overestimate of the number of person-years of follow-up for pancreatic cancer. Nevertheless, the observed levels of semaglutide use from 2018-2020 in Denmark, Norway and Sweden contribute a considerable number of patients with several years of potential follow-up before the study period ends in 2023.

Table 3 Number of unique* patients exposed to semaglutide (Ozempic® and Rybelsus®) in available databases in countries included in the study

Country	Population covered by databases	First commercial launch dates for semaglutide (Ozempic®)	Data coverage				
					2018	**2019**	**2020**
Denmark	Nationwide, 5.7 million individuals	20 August 2018	2018 - 2020	**Unique users***	5,747	21,900	38,280
				Male	3,319	12,684	21,825
				Female	2,428	9,216	16,455
				18-24y	20	65	139
				25-44y	493	1,940	3,332
				45-64y	2,846	10,749	18,322
				65-79y	2,220	8,314	14,726
				80+y	168	832	1,761
					2018**	**2019**	**2020**
Norway***	Nationwide, 5.4 million individuals	01 February 2019	2018 - 2020	**Unique users***	18	5,252	14,464
				Male	6	2,912	7,767
				Female	12	2,340	6,697
				20-24y	-	33	105
				25-44y	-	584	1,852
				45-64y	-	2,774	7,514
				65-79y	-	1,673	4,497
				80+y	-	188	496
					2018	**2019**	**2020**
Sweden***	Nationwide, 10.1 million individuals	26 October 2018	2018 - 2020	**Unique users***	827	13,599	32,206
				Male	522	7,968	18,795
				Female	305	5,631	13,411
				20-24y	5	52	127
				25-44y	77	1,123	2,731
				45-64y	409	6,473	14,874
				65-79y	311	5,419	13,005
				80+y	25	532	1,469

* Unique users only within the specific calendar year. Data on unique users across calendar years are currently not available.

** Age-stratification in Norway not possible due to small counts

***Publicly available data from Norway and Sweden include age stratification by the age group 15-19 years. As use in patients below 18 years of age is outside the approved label of Ozempic® and Rybelsus® and due to the inclusion criteria in the study requiring age ≥18 years, users of semaglutide in age groups under 20 years are not listed in the table nor included in the total number of unique users.

Table 4 Status on data access in collaborating countries

Countries	Status
Denmark	Application for data access in Denmark is approved and data on semaglutide users from the Danish commercial launch date has been extracted.
Norway	Application for the approvals for the full linked data including ethical approvals and data ordering 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 since last progress report

Date	Participants	Purpose	Main agenda points
01 June 2021 Virtual meeting	University of Southern Denmark (SDU) Karolinska Institutet (KI) Norwegian Institute of Public Health (NIPH) Novo Nordisk	SAP development Plan for progress report 2	Status on Common Data Model (CDM) Discussion of SAP Discussion of propensity score implementation Validation of Danish cancer data Progress report 2

2.4 Status

The NN9535-4447 amended study protocol version 2.0 was approved by PRAC 25 March 2021 (Ozempic® (EMEA/H/C/004174/MEA/002.2) and Rybelsus® (EMEA/H/C/004953/MEA/002.1)).

The study is progressing as planned in terms of product utilisation, data applications, data access and the research collaboration.

The number of patients exposed to semaglutide 2018-2020 fulfils the expectations specified in the protocol. The uptake of semaglutide 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 SDU entity submitted the ENCePP seal on 09 October 2020. The EnCePP seal was awarded 17 December 2020.

Application for data access in Denmark is approved and access to data on semaglutide users is established in Denmark. This early access to Danish data facilitates the development of the common data model and will facilitate the development of the programming of analyses.

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