

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	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): <i>26 January 2021</i>
Sponsor	Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark
Data cut-off date	The cut-off for the data presented in the report is <i>31 December 2022</i> in Denmark and Sweden, <i>and 30 September 2022</i> in Norway.

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1 Background

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

The cut-off for the data presented in the report is 31 December 2022 in Denmark and Sweden, and 30 September 2022 in Norway.

The NN9535-4447 study is a post-authorisation safety study (PASS). 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, Pharmacy and Environmental Medicine, 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 Department of Chronic Diseases, Norwegian Institute of Public Health, 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.

The study progress report is based on publicly available aggregated data, and individual-level data sources for Norwegian data from 2022. The data cut-off is 31 December 2022 in Denmark and Sweden, and 30 September 2022 in Norway.

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.

2.2 Enrolling countries

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

Country	Department, Institute	Abbreviation	Role
Denmark	Clinical Pharmacology, Pharmacy and Environmental Medicine, 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	Department of Chronic Diseases, Norwegian Institute of Public Health, Oslo	NIPH	Collaborator

The agreement between Novo Nordisk and University of Southern Denmark is currently being updated. Subcontracts between SDU and research partners KI and NIPH are in place.

2.3 Study Progress

For the purpose of the progress report, data are extracted from publicly available databases in Norway, Sweden, and Denmark while Norwegian data from 2022 is based on individual-level data sources. The databases include information on number of individual semaglutide users by sex and age. The cut-off for the data presented in the report is 31 December 2022 in Denmark and Sweden, and 30 September 2022 in Norway.

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	2021	2022
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	85,000	117,000
Number of unique patients exposed to semaglutide as observed in the databases. Total population (Denmark, Norway, and Sweden)	6,592	40,751	84,950	152,979	235,592

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 2018-2022 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	2021	2022
Denmark	Nationwide, 5.7 million individuals	20 August 2018	2018 - 2022	Unique users*	5,747	21,900	38,280	59,493	91,098
				Male	3,319	12,684	21,825	32,912	46,624
				Female	2,428	9,216	16,455	26,581	44,474
				18-24y	20	65	139	301	718
				25-44y	493	1,940	3,332	5,711	11,578
				45-64y	2,846	10,749	18,322	28,425	44,402
				65-79y	2,220	8,314	14,726	22,083	30,132
				80+y	168	832	1,761	2,973	4,268
Norway***	Nationwide, 5.2 million individuals	1 February 2019	2018 - 2022		2018**	2019	2020	2021	2022 [‡]
				Unique users*	18	5,252	14,464	36,889	61,100
				Male	6	2,912	7,767	17,895	26,794
				Female	12	2,340	6,697	18,994	34,306
				20-24y	-	33	105	302	18-39y 7,754
				25-44y	-	584	1,852	5,822	40-59y 28,148
				45-64y	-	2,774	7,514	19,457	60-79y 23,454
				65-79y	-	1,673	4,497	10,208	
Sweden***	Nationwide, 10.1 million individuals	26 October 2018	2018 - 2022		2018	2019	2020	2021	2022
				Unique users*	827	13,599	32,206	56,597	83,394
				Male	522	7,968	18,795	32,295	46,399
				Female	305	5,631	13,411	24,302	36,995
				20-24y	5	52	127	208	334
				25-44y	77	1,123	2,731	4,887	7,989
				45-64y	409	6,473	14,874	25,321	37,200
				65-79y	311	5,419	13,005	22,906	32,666
				80+y	25	532	1,469	3,275	5,205

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

** Age-stratification for 2018 in Norway not possible due to small counts

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***Publicly available data from Norway (until 2022) 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.

¥Unique users from 1 January to 30 September 2022. Data from 2022 allows for another age stratification than in previous years.

Table 4 Status on data access in collaborating countries

Countries	Status
Denmark	Data has been extracted. Final data extraction including the final study population is expected in Q1 2024.
Norway	Ethical approval has been granted and data has been received from 3 of 6 registers.
Sweden	Ethical approval has been granted. Intermediate data has been extracted and are available. Final data extraction requires separate data application to the National Board of Health and Welfare and Statistics Sweden, which will be prepared end of 2023/beginning of 2024.

Table 5 Meetings since last progress report

Date	Participants	Purpose	Main agenda points
26 June 2023 Virtual meeting	University of Southern Denmark (SDU) Karolinska Institutet (KI) Norwegian Institute of Public Health (NIPH) Novo Nordisk	To discuss table shells/figures and status on transformation of data into common data model.	To discuss table shells and figures. To take a status on transformation of data into common data model.

2.4 Status

The NN9535-4447 study is progressing as planned in terms of product utilisation, granting of ethical approvals, data access in all countries, and development of a common data model.

The number of patients exposed to semaglutide 2018-2022 fulfils the expectations specified in the protocol. The large 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 research collaboration is well established and is progressing in terms of development of shell tables and figures, and transformation of Norwegian and Swedish data into a common data model developed by the coordinating study entity in Denmark.