

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	<i>31 December 2021</i> 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 3 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 2021.

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 including data access.

The study progress report is based on publicly available aggregated data, and individual-level data sources for Norwegian data from 2021. The data cut-off is 31 December 2021 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 original study protocol, the Statistical Analysis Plan (SAP) was planned to be finalized in Q4 2020. Due to an amendment of the study protocol (as outlined in progress report no. 2) the finalization of the SAP was postponed to Q4 2021. In accordance with the postponement, the first version of the final SAP was finalized in 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, 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 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 while Norwegian data from 2021 is based on individual-level data

sources. The databases include information on number of individual semaglutide users by sex and age. The data cut-off date is 31 December 2021.

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
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
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

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 2018-2021 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
Denmark	Nationwide, 5.7 million individuals	20 August 2018	2018 - 2021	Unique users*	5,747	21,900	38,280	59,493
				Male	3,319	12,684	21,825	32,912
				Female	2,428	9,216	16,455	26,581
				18-24y	20	65	139	301
				25-44y	493	1,940	3,332	5,711
				45-64y	2,846	10,749	18,322	28,425
				65-79y	2,220	8,314	14,726	22,083
				80+y	168	832	1,761	2,973
					2018**	2019	2020	2021
Norway***	Nationwide, 5.2 million individuals	1 February 2019	2018 - 2021	Unique users*	18	5,252	14,464	36,889
				Male	6	2,912	7,767	17,895
				Female	12	2,34	6,697	18,994
				20-24y	-	33	105	302
				25-44y	-	584	1,852	5,822
				45-64y	-	2,274	7,514	19,457
				65-79y	-	1,673	4,497	10,208
				80+y	-	188	496	1,100
					2018	2019	2020	2021
Sweden***	Nationwide, 10.1 million individuals	26 October 2018	2018 - 2021	Unique users*	827	13,599	32,206	56,597
				Male	522	7,968	18,795	32,295
				Female	305	5,631	13,411	24,302
				20-24y	5	52	127	208
				25-44y	77	1,123	2,731	4,887
				45-64y	409	6,473	14,874	25,321
				65-79y	311	5,419	13,005	22,906

Ozempic and Rybelsus
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Novo Nordisk

				80+y	25	532	1,469	3,275
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* 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

***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	Data has been extracted.
Norway	Ethical approval has been granted. Applications for data access is in preparation.
Sweden	Ethical approval has been granted. Applications for data access 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
17 January 2022	University of Southern Denmark (SDU)	To discuss and clarify comments to the first version of final statistical analysis plan.	To discuss comments related to study design as described in the statistical analysis plan.
Virtual meeting	Karolinska Institutet (KI)		To discuss and agree on codes used in the definition of covariates.
	Norwegian Institute of Public Health (NIPH)		
	Novo Nordisk		

2.4 Status

The NN9535-4447 study is progressing as planned in terms of product utilisation, data access in Denmark, data applications in Norway and Sweden, granting of ethical approvals, and the research collaboration.

The number of patients exposed to semaglutide 2018-2021 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 finalization of the statistical analysis plan and development of the common data model.