Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05891496
Sponsor trial ID:	NN6535-7519
Official title of study:	A randomised double-blind placebo-controlled clinical study investigating the effects of semaglutide s.c. once-weekly versus placebo on central and peripheral inflammation in participants with Alzheimer's disease
Document date*:	06 November 2024

*Document date refers to the date on which the document was most recently updated.

Protocol

Protocol Title:
A randomised double-blind placebo-controlled clinical study investigating the effects of semaglutide s.c. once-weekly versus placebo on central and peripheral inflammation in participants with Alzheimer's disease

Short Title:
A research study looking at the effect of semaglutide on the immune system and other biological processes in people with Alzheimer's disease

Substance name: Semaglutide s.c. once-weekly

Protocol version number: 4.0

Protocol version applicability: Global

Universal Trial Number: U1111-1283-8743

EU CT Number: 2023-506825-13

IND Number: 146391

Redacted protocol
includes redaction of company confidential information.

Study Phase: 3b

In the following, Novo Nordisk A/S and its affiliates will be stated as "Novo Nordisk".

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol version 4.0	06 November 2024	All
Protocol version 3.0	19 June 2024	All
Protocol version 2.0	26 April 2023	Denmark, Italy, Sweden, Switzerland
Original protocol version 1.0	14 December 2022	All

Protocol version 4.0 (06 November 2024)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.[1]

Overall rationale for preparing protocol, version 4.0:

Protocol version 4.0 dated 06 November 2024, has been updated to incorporate a new safety signal. Additional changes include, change in method resulting in a different unit for an exploratory endpoint, addition of a lower maintenance dose as well as updates to internal protocol guidelines. An overview of the changes is shown in the table below.

New text is written as *italic* and deleted text is written with ~~strikethrough~~.

Section # and name	Description of change	Brief rationale
Section 2.3.1 Risk Assessment	Added new text in Table 2-1 **Potential risk of clinical significance** *Aspiration in association with general anesthesia or deep sedation* **Summary of data/rationale for risk** *There is currently insufficient evidence that GLP-1 RAs increase the risk of aspiration in association with general anesthesia or deep sedation. However, given that GLP-1 RAs may cause a delay in gastric emptying leading to retention of gastric contents, there is a theoretical risk of aspiration in patients undergoing operative procedures under general anesthesia or deep sedation. Aspiration in association with general anesthesia or deep sedation is potentially serious as it may result in severe complications.* **Mitigation and monitoring strategy** *Patients should be informed of the risk of aspiration in association with general anaesthesia or deep sedation, and inform their doctor that they are taking a GLP-1 RA when undergoing planned general anesthesia or deep sedation. Doctors should follow local anesthesiologic guidelines on preoperative management of patients treated with GLP-1 RAs when possible. If anesthesia-related aspiration is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.*	Based on combined responses from Health Authorities and the plausible biological mechanism for aspiration in association with general anaesthesia or deep sedation being delayed gastric emptying, a new safety signal of "Aspiration in association with general anesthesia or deep sedation" has been validated.

Section # and name	Description of change	Brief rationale
Section 3.1 Objectives and endpoints	Unit for exploratory endpoint "To compare the effects of semaglutide s.c. 1.0 mg once-weekly versus placebo on the T cell receptor profiles in CSF and plasma in participants with Alzheimer's disease" changed from "Count of clonally expanded T cells" to "*Morisita-Horn index*"	Change in method for deriving changes in T cell clonal landscape, resulting in a different unit
Section 6.1.3 Dose escalation	New text added: [redacted]	To allow lower maintenance dose of 0.25 mg once-weekly
Section 7.1.1 Study intervention discontinuation criteria	Deleted text: Final study intervention accountability must be performed even if the participant is not able to come to the site. Discontinuation of treatment must be registered in the RTSM/~~IWRS~~.	For correctness
Section 7.2 Participant discontinuation/withdrawal from the study	Deleted text: ~~Study participants are expected to stay in the study for the entire study duration, irrespective of their adherence to allocated study intervention or adherence to the protocol in general. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for key assessments; see Section 7.1 for details.~~ New text added: If a participant withdraws consent or is withdrawn by the investigator after randomisation….See the flowchart for data to be collected. *The end of study form must be completed.* *The withdrawal date is considered to be the participant's last visit, assessment or contact in the study, whichever is the latest.* If the participant withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent for the purpose of the study or scientific research. *This will also apply in any country(ies) relying on explicit informed consent as legal basis for processing personal data. If a participant wants to exercise any of his/her rights, he/she must follow the description in the 'Agreement to take part' form (See Section 10.1.3).*	Alignments with updates to internal protocol guidelines

Section # and name	Description of change	Brief rationale
Section 10.1.1 Regulatory and ethical considerations	New text added: Regulatory authorities will receive the clinical trial application, protocol amendments/*modifications*, reports on SAEs, and the CSR according to national requirements. Any amendments/*modifications* to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate safety hazard to study participants. *In case of changes made to eliminate an immediate safety hazard, the actions must be reported to Novo Nordisk immediately (within 24 hours after the action was taken).* Before a site is allowed to start screening participants, written notification from Novo Nordisk must be received. *The list of investigator responsibilities below reflects global GCP requirements. Certain activities related to IRB/IEC submission can be carried out by the sponsor, in accordance with local or regional regulatory requirements.*	Alignments with updates to internal protocol guidelines
Section 10.1.10 Retention of clinical study documentation	New text added: Participant's medical records must be kept for the maximum period permitted by the hospital, institution or private practice. *Novo Nordisk will retain study documentation for 25 years or longer as required by local law, or as long as the information contributes to scientific purposes or product safety.*	Alignments with updates to internal protocol guidelines
Throughout the document	Deleted text: RTSM~~/IWRS~~	For correctness

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Protocol attachment I: Global list of key staff and relevant departments and suppliers
Protocol attachment II: Country list of key staff and relevant departments

1 Protocol summary

1.1 Synopsis

This is an interventional, randomised, parallel-group, double-blind, placebo-controlled, multi-centre, multi-national study designed to evaluate the effects of semaglutide 1.0 mg versus placebo (randomised 1:1), both administered s.c. once-weekly and added to standard of care, on central and peripheral inflammation in participants with mild cognitive impairment (MCI) or mild dementia, both of the Alzheimer's type.

Rationale:

Semaglutide exhibits glucagon-like peptide-1 (GLP-1) receptor mediated effects across multiple pathways that may impact the pathophysiological processes underlying Alzheimer's disease. GLP-1 receptors are expressed in the brain, blood vessels, cells of the immune system, kidney, heart and pancreas, and GLP-1 receptor activation has been shown to have direct protective effects on neurons,[2, 3] attenuate neuroinflammation,[4-6] reduce peripheral inflammation[7] and oxidative stress,[8] while improving blood-brain barrier integrity[4] and synapse viability[9, 10]. Accordingly, the leading hypothesis for the mode of action of semaglutide in Alzheimer's disease is that it has multifaceted actions affecting neuroinflammation, peripheral inflammation, oxidative stress, blood-brain barrier integrity and other pathways which may reduce neurodegeneration in Alzheimer's disease pathology. This hypothesis is further supported by a nonclinical study in a lipopolysaccharide (LPS)-induced mouse model of neuroinflammation, which showed that semaglutide lowered hippocampal neuroinflammation by significantly decreasing the area of microglia and attenuating co-expressed inflammatory genes in LPS/semaglutide-treated mice (data on file).[6, 11] Additionally, a recent study suggested that GLP-1 receptor expression in T cells could play an anti-inflammatory role.[12] Furthermore, a 14-35% and a 50-60% reduction in C-reactive protein was observed in the type 2 diabetes mellitus (T2DM) and obesity development programmes, respectively, indicating systemic anti-inflammatory effects with semaglutide.[7, 13]

The aim of this exploratory study is to investigate the effect of semaglutide on central and peripheral inflammation in participants with Alzheimer's disease. This will be done by investigations of; *i*) gene expression changes in cells in cerebrospinal fluid (CSF) and blood, and *ii*) biomarkers and proteomics. In addition, safety will be evaluated.

Objectives and endpoints:

The objectives and endpoints of this exploratory study are summarised in the table below.

Objectives	Endpoints		
Primary	**Title**	**Time frame**	**Unit**
To investigate the effect of semaglutide s.c. 1.0 mg once-weekly versus placebo on central and peripheral inflammation in participants with Alzheimer's disease	*Co-primary:*		
	Change in gene expression assessed by scRNAseq (cells in CSF)	From baseline (week 0) to visit 5 (week 12)	Number of differentially expressed genes
	Change in gene expression assessed by scRNAseq (cells in blood)	From baseline (week 0) to visit 5 (week 12)	Number of differentially expressed genes
Secondary	**Title**	**Time frame**	**Unit**
To compare the effects of semaglutide s.c. 1.0 mg once-weekly versus placebo on safety and tolerability in participants with Alzheimer's disease	*Supportive secondary:*		
	Number of treatment emergent adverse events (TEAEs)	From baseline (week 0) to visit 5 (week 12)	Number of events
To evaluate the effects of semaglutide s.c. 1.0 mg once-weekly on safety and tolerability in participants with Alzheimer's disease	Number of treatment emergent adverse events (TEAEs)	From baseline (week 0) to end of treatment (week 64)	Number of events
To evaluate the steady state pharmacokinetics of semaglutide s.c. 1.0 mg once-weekly in participants with Alzheimer's disease	Weekly average semaglutide concentration (C_{avg}) based on population PK analysis	From visit 3 (week 4) to end of treatment (week 64)	nmol/L

Abbreviations: C_{avg} = average concentration; CSF = cerebrospinal fluid; PK = pharmacokinetics; s.c. = subcutaneous; scRNAseq = single-cell ribonucleic acid sequencing; scTCRseq = single-cell T cell receptor sequencing.

Overall design:

The study consists of the following periods:

- Screening period: up to 8 weeks
- Study intervention periods
  - *Study intervention period 1* (double-blind): 12 weeks
  - *Study intervention period 2* (open-label): 52 weeks
- Follow-up period: 5 weeks

The planned study duration for the individual participant will be up to 77 weeks (including screening period).

Study intervention groups and duration:

The following study intervention will be supplied by Novo Nordisk A/S:

- semaglutide 1.34 mg/mL, subcutaneous, solution for injection, 1.5 mL pre-filled PDS290 (DV3326-C3) pen-injector
- placebo, subcutaneous, solution for injection, 1.5 mL pre-filled PDS290 (DV3326-C3) pen-injector

Number of participants:

The sample size of 24 participants randomised 1:1 was chosen to enable 10 completing participants per arm, with a 20% drop-out rate.

Participant characteristics:

Key inclusion and exclusion criteria are summarised below:

Key inclusion criteria

- Male or female, aged 55-75 years (both inclusive) at the time of signing the informed consent.
- MCI or mild dementia of the Alzheimer's type according to the NIA-AA 2018 criteria.
- Clinical dementia rating (CDR) global score of 0.5 or 1 at screening (visit 1).
- Amyloid positivity established with either historical amyloid positron emission tomography (PET) *or* historical CSF $A\beta_{1-42}$ *or* historical CSF $A\beta_{1-42}/A\beta_{1-40}$ (historical data within the last 5 years) *or* blood sample for amyloid biomarker ($A\beta_{42}/A\beta_{40}$ ratio and p-tau_{217}/np-tau_{217} ratio) at screening (visit 1).
  For definition of amyloid positivity, see Section 8.1.2
- Treated with acetylcholinesterase inhibitors (approved for the treatment of Alzheimer's disease) and on stable dose for > 90 days before screening (visit 1).

Key exclusion criteria

- Brain magnetic resonance imaging (MRI) scan suggestive of clinically significant structural central nervous system (CNS) disease confirmed by local read (e.g., cerebral large-vessel disease [large vessel (cortical) infarcts >10 mm in diameter], prior macro-haemorrhage [>1 cm^3], cerebral vascular malformations, cortical hemosiderosis, intracranial aneurism(s), intracranial tumours, changes suggestive of normal pressure hydrocephalus).
- Brain MRI scan suggestive of significant small vessel pathology confirmed by local read and defined as >1 lacunar infarct and/or white matter hyperintensity (WMH) Fazekas[14] scale >2, (WM >20 mm) in the deep white matter and periventricular regions.
- History or evidence of autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, lupus, glomerulonephritis, psoriasis (but not limited to):
  - Any other medical condition that would require use of systemic corticosteroids or immunosuppressants or immunostimulants in the 12 months prior to screening (visit 1)
- Received a vaccine product (including booster) 4 weeks prior to screening (visit 1) or expected to receive a vaccine product (including booster) before visit 5.
- Use of any systemic immunomodulating drugs (small molecules and/or biologics) in the last 12 months prior to screening (visit 1) or anticipated use of such drugs during study intervention period 1 (i.e., during the first 12 weeks of treatment until visit 5), such as corticosteroids for systemic use, immunostimulants and immunosuppressants.

Data monitoring committee:

No

1.2 Flowchart

Procedure	Protocol section	Screening period	Randomisation	Intervention/treatment period								End-of-treatment	End of study
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of visit (weeks)		-8	0	4	8	12	16	20	24	36	48	64	V11+5
Visit window (days)		+56	0	+7	+7	+10	±7	±7	±7	±7	±7	±7	+7
PARTICIPANT RELATED INFO/ASSESSMENTS													
Informed consent[a]	10.1.3	X											
Demography[b]	8.11	X											
Hand out ID card		X											
Hand out and instruct in dosing diary	8.2.3		X	X	X	X	X	X	X	X	X		
Dosing diary review and recording	8.2.3			X	X	X	X	X	X	X	X	X	
Eligibility criteria	5	X	X										
Randomisation	5.5		X										
Concomitant medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X
Discontinuation criteria	7.1			X	X	X	X	X	X	X	X	X	
Medical history/Concomitant illness	8.3.1	X	X										
Historical amyloid biomarker (PET/CSF)[c]	8.1.2.1	X											
Childbearing potential	8.4.5	X											
Urine pregnancy test[d]	8.4.5	X										X	X
Tobacco and nicotine products use[e]	8.12		X										
Alcohol habits[f]	8.1.4	X											
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12

Procedure	Protocol section	Screening period	Randomisation	Intervention/treatment period								End-of-treatment	End of study
Timing of visit (weeks)		-8	0	4	8	12	16	20	24	36	48	64	V11+5
Visit window (days)		+56	0	+7	+7	+10	±7	±7	±7	±7	±7	±7	+7
CLINICAL OUTCOME ASSESSMENTS													
CDR	8.1.3	X											
MRI scan[g]	8.1.1	X											
Lumbar puncture (CSF collection)[h]	8.2.2		X			X							
C-SSRS	8.1.5	X	X	X	X	X	X	X	X	X	X	X	X
ECG	8.3.5		X			X						X	
Height	8.3.3	X											
Body weight	8.3.3	X	X			X			X	X	X	X	
Physical examination and neurological assessment	8.3.2	X				X						X	
Vital signs	8.3.4	X	X[i]	X	X	X[i]	X	X	X			X	X
Adverse events and other safety reporting	8.4, 10.3		X[j]	X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS (non-fasting)													
Blood sample for amyloid biomarker ($A\beta_{42}/A\beta_{40}$ ratio and p-tau_{217} /np-tau_{217} ratio)	8.1.2	X											
Blood sample for biomarkers related to semaglutide action as well as neuroinflammatory, neurodegenerative and Alzheimer-related biomarkers[k]	8.8		X			X			X			X	
Blood sample for scRNAseq and scTCRseq	8.8	X	X			X							
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of visit (weeks)		-8	0	4	8	12	16	20	24	36	48	64	V11+5

Procedure	Protocol section	Screening period	Randomisation	Intervention/treatment period								End-of-treatment	End of study
Visit window (days)		+56	0	+7	+7	+10	±7	±7	±7	±7	±7	±7	+7
Blood sample for proteomics	8.8		X			X							
CSF sample for amyloid biomarker ($A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ ratio)	8.8		X										
CSF sample for biomarkers related to semaglutide action as well as neuroinflammatory, neurodegenerative and Alzheimer-related biomarkers[k]	8.8		X			X							
CSF sample for scRNAseq and scTCRseq	8.8		X			X							
CSF sample for proteomics	8.8		X			X							
CSF sample for semaglutide concentration[l]						X							
APOE genotype[m]	8.7.1		X										
Infection serology[n]	8.3.6	X											
eGFR (CKD-EPI)[15]	8.3.6	X				X			X			X	
Vitamin B12, Folate, Thyroid Stimulating Hormone	8.3.6	X											
hs-CRP	8.3.6	X	X			X			X			X	
HbA_{1c}	8.3.6	X				X							
Biochemistry	8.3.6	X				X			X			X	
Haematology	8.3.6	X	X			X			X			X	
Coagulation	8.3.6	X											
PK sampling	8.5			X	X	X	X		X			X	X
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Timing of visit (weeks)		-8	0	4	8	12	16	20	24	36	48	64	V11+5

Procedure	Protocol section	Screening period	Randomisation	Intervention/treatment period								End-of-treatment	End of study
Visit window (days)		+56	0	+7	+7	+10	±7	±7	±7	±7	±7	±7	+7
Blood sample for immunogenicity assessment[o]	8.9		X	X	X	X	X		X			X	X
Blood sample for future analysis[p] (*optional*)	8.10		X			X			X			X	
CSF sample for future analysis[p] (*optional*)	8.10		X			X							
STUDY MATERIAL													
Training in administration of study intervention and dosing instructions and supervised administration of study intervention during the study visit[q]	6.1		X	X	X	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]		
Drug dispensing			X	X		X	X		X	X	X		
OTHER ACTIVITIES													
Ensure updated contact persons list		X	X	X	X	X	X	X	X	X	X	X	
End of study													X

Notes:

[a] Informed consent should be obtained from both the participant and the study partner (Appendix 1, Section 10.1.3);

[b] Demography for the participant consists of: birth, sex, ethnicity and race (according to local regulation), and years of education. Ethnicity and race must be self-reported by the participant. Demography for the study partner consists of: birth and relationship to the participant (according to local regulation). Local requirements may apply. Switzerland: see country-specific requirements (Appendix 8, Section 10.8);

[c] Use of historical amyloid PET, CSF $A\beta_{1-42}$ or CSF $A\beta_{1-42}/A\beta_{1-40}$ assays up to 5 years old is allowed for inclusion (inclusion criterion #7) (Section 8.1.2);

[d] Only applicable for women of childbearing potential. Urine dipstick pregnancy test (urine HCG) should also be performed at any time during the trial if menstrual period is missed, and/or according to local regulations/law. Local requirements may apply, see country-specific requirements (Appendix 8, Section 10.8);

[e] Tobacco use is defined as smoking at least one cigarette or equivalent daily;

[f] Alcohol consumption (current alcohol use [units per week]);

[g] MRI is to be performed after completion of all study-related assessments at visit 1 and in due time for the result to be ready before randomisation (visit 2);

[h] Collect information on recent (within 3 days prior the lumbar puncture procedure) episodes of fever, cold, hay fever attacks, allergies, head trauma with loss of consciousness, and use of painkillers (Section 8.2.2). At the investigator's discretion, the lumbar puncture may be delayed for up to 10 days, if the participant within the last week has experienced signs of infections or has complaints related to altered immune responses.

[i] Skin temperature should be measured prior to lumbar puncture at visit 2 and visit 5;

[j] Only AEs/SAEs with an onset after the lumbar puncture performed at visit 2 should be reported. Conditions/concomitant illness present before the lumbar puncture at visit 2 should be recorded as medical history/concomitant illness (Section 8.3.1);

[k] Biomarkers will be defined in the Statistical Analysis Plan (SAP) depending on the availability of validated biomarkers before database lock (DBL);

[l] Analysis will be performed only if a validated reliable assay is available at the end of study;

[m] Individual test results will not be given to participants or communicated to the study sites;

[n] Infection serology will include screening for HIV (exclusion criterion #12), hepatitis B and C (exclusion criterion #11);

[o] All samples must be drawn prior to administration of study intervention if administration of study intervention is planned on the sampling day.

[p] Separate informed consent required;

[q] At visit 2, the initial administration of study intervention will be performed by the study partner under supervision of the investigator, during the study visit after all assessments have been completed;

[r] As needed.

Abbreviations: CKD-EPI = chronic kidney disease – epidemiology collaboration; CDR = clinical dementia rating ; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicidal Severity Rating Scale ; ECG =; eGFR = estimated glomerular filtration rate; hs-CRP = high sensitivity C-reactive protein; HbA_{1c} = glycosylated haemoglobin; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; np = non-phosphorylated; PK = pharmacokinetics; scRNAseq = single-cell ribonucleic acid sequencing; scTCRseq = single-cell T cell receptor sequencing.

2 Introduction

Semaglutide is a potent human GLP-1 analogue that acts as a GLP-1 RA, with a long half-life (approximately 1 week) suitable for once weekly s.c. dosing. Novo Nordisk has developed semaglutide for the treatment of T2DM and for which marketing approval has been received by the U.S. Food and Drug Administration (FDA), the European Commission (EC) and several other countries (brand name Ozempic® for semaglutide injected s.c., and Rybelsus® for oral semaglutide). Further, marketing approval has been received by the FDA and the EC for the treatment of chronic weight management (brand name Wegovy™ for semaglutide injected s.c.).

There is growing evidence supporting semaglutide, and GLP-1 RAs as a class, to have therapeutic potential in Alzheimer's disease. These include randomised controlled clinical study data showing that in people with Alzheimer's disease a GLP-1 RA liraglutide reduced both cognitive decline[4, 5, 16] and decline in cerebral glucose metabolism[10] (CMRglc, a marker of neurodegeneration). Data from CVOTs in T2DM showed that GLP-1 RAs lowered the risk of all-cause dementia diagnosis[17] and reduced cognitive decline[18] accompanied with a decrease in NfL levels (a marker of neurodegeneration) in participants with high levels of NfL at baseline[19]. Furthermore, liraglutide reduced cognitive decline[20] in T2DM patients and improved short-term memory in people with obesity and prediabetes or early T2DM[21]. These clinical data are further supported by real-world evidence data showing lower risk of all-cause dementia[17, 22] and dementia due to Alzheimer's disease[23] in T2DM patients treated with GLP-1 RAs. In addition, a genetic variation in the gene encoding the GLP-1 receptor resulting in increased receptor function, is associated with a lower risk of Alzheimer's disease.[24]

Semaglutide exhibits GLP-1 receptor mediated effects across multiple pathways that may impact the pathophysiological processes underlying Alzheimer's disease. GLP-1 receptors are expressed in the brain, blood vessels, cells of the immune system, kidney, heart and pancreas, and GLP-1 receptor activation has been shown to have direct protective effects on neurons,[2, 3] attenuate neuroinflammation,[4-6] reduce peripheral inflammation[7] and oxidative stress,[8] while improving blood-brain barrier integrity[4] and synapse viability[9, 10]. Furthermore, semaglutide reduces the time to first occurrence of stroke, an association driven by a significant reduction in cerebral small vessel occlusion.[25] Overall, both clinical and nonclinical data suggest that semaglutide has multifaceted effects that affect neuronal integrity and functions relevant for Alzheimer's disease pathophysiology.

2.1 Study rationale

Two phase 3a randomized, double-blind, placebo-controlled studies are currently investigating the effect and safety of oral semaglutide in people with early Alzheimer's disease, i.e., MCI or mild dementia, both of the Alzheimer's type (NN6535-4725 and NN6535-4730, hereafter referred to as the evoke^{+} and evoke studies). The leading hypothesis for the mode of action of semaglutide in Alzheimer's disease is that it has multifaceted actions affecting neuroinflammation, peripheral inflammation, oxidative stress, blood-brain barrier integrity and other pathways which may reduce neurodegeneration in Alzheimer's disease pathology. This hypothesis is further supported by a nonclinical study in a LPS-induced mouse model of neuroinflammation, which showed that semaglutide lowered hippocampal neuroinflammation by significantly decreasing the area of microglia and attenuating co-expressed inflammatory genes in LPS/semaglutide-treated mice (data

on file).[6, 11] Additionally, a recent study suggested that GLP-1 receptor expression in T cells could play an anti-inflammatory role.[12] Furthermore, a 14-35% and a 50-60% reduction in CRP was observed in the T2DM and obesity development programmes, respectively, indicating systemic anti-inflammatory effects with semaglutide.[7, 13]

The aim of this exploratory study is to investigate the effect of semaglutide on central and peripheral inflammation in participants with Alzheimer's disease. This will be done by investigations of; *i*) gene expression changes in cells in CSF and blood, and *ii*) biomarkers and proteomics. In addition, safety will be evaluated.

A s.c. formulation of semaglutide is selected in this small exploratory study for practical reasons and to secure a lower variability in exposure following administration compared to that achieved with the oral formulation.

2.2 Background

Dementia is a rapidly growing public health concern causing a significant global socioeconomic impact. Worldwide, around 50 million people are currently living with dementia with a projected increase to approximately 152 million people by the year 2050.[26] Neurodegeneration due to Alzheimer's disease underlies the majority of dementia cases.[27] Clinically, the continuum of disease progression from MCI to mild, moderate and severe dementia is accompanied by gradual loss of cognitive function and increasing difficulties in performing activities of daily living.[28] Effective treatments for Alzheimer's disease that can slow disease progression in a convenient and safe way are urgently needed given the significant burdens of this disease on both a personal and societal level.

Neuroinflammation plays a part of the pathophysiology in Alzheimer's disease, which has been shown in neuroimaging studies,[29] longitudinal biomarker studies[30] and by enrichment of Alzheimer's disease GWAS risk genes in immune pathways.[31] Furthermore, observational studies suggest that systemic inflammation is associated with risk of Alzheimer's disease onset and disease progression.[32, 33] Importantly, single-cell gene expression[34] and proteomics signatures[35, 36] now provide unprecedented ways to investigate the transcriptional and proteomic changes in response to treatment with relatively few study participants. This study will include participants with MCI or mild dementia, both of the Alzheimer's type, to be able to explore the effect of semaglutide on central and peripheral inflammation.

Semaglutide and liraglutide are both GLP-1 RAs designed to bind to human serum albumin, while semaglutide was further optimised to provide a half-life suitable for once weekly subcutaneous injection, and once daily oral administration. The potential effects of liraglutide and semaglutide on cognition and related mechanisms stem from clinical data from a real-world study and post-hoc analysis based on randomised controlled studies in participants with T2DM, which have indicated that treatment with GLP-1 RAs, liraglutide and semaglutide, reduces the risk of dementia.[37, 38] Furthermore, in patients with Alzheimer's disease, a randomised controlled study showed that liraglutide prevented the decline in cerebral glucose metabolism (CMRglc, a marker of neurodegeneration).[10] Randomised controlled studies in patients with T2DM have further shown a reduction in MACE including stroke following treatment with semaglutide,[39] an effect hypothesised to be mediated through attenuation of atherosclerotic plaque progression and reducing inflammation

in the plaque by semaglutide.[5, 40, 41] Semaglutide and liraglutide have also been investigated in relevant nonclinical models on Alzheimer's disease, and inflammation. These studies showed improved memory function,[42] reduced phospho-tau accumulation,[42] and reduced systemic and neuroinflammation.[5, 40, 41]

To provide further information for an evidence-based mode of action of semaglutide, an unbiased assessment of gene expression changes at the single-cell level of CSF and blood cells, respectively, will be performed. An explorative investigation of accompanying proteomic changes and biomarkers on CSF and plasma will also be included in this study. The selected individual biomarkers reflect both established markers demonstrated to be involved in semaglutide's mode of action in animal studies, as well as markers linked to Alzheimer's disease risk and progression, inflammation, and oxidative stress. Furthermore, this study is being conducted to evaluate the safety of semaglutide s.c. for the treatment of participants with MCI or mild dementia, both of the Alzheimer's type.

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide s.c. may be found in the current edition of the investigator's brochure[43] or updates thereof.

2.3.1 Risk assessment

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Study intervention: semaglutide s.c. once-weekly		
Gastrointestinal disorders	Consistent with other GLP-1 RAs, the most frequent AEs with semaglutide are gastrointestinal (such as nausea, vomiting and diarrhoea). In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. In participants treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating participants with impaired renal function as it may cause a deterioration of renal function.	Clinical studies have shown that a low starting dose and gradual dose escalation mitigates the risk of developing gastrointestinal symptoms. Participants with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion.
Allergic reactions	As with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions, including serious allergic reactions such as angioedema and anaphylactic reactions.	As a precaution, participants with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this study. In addition, participants will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the study intervention occurs.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Aspiration in association with general anesthesia or deep sedation	There is currently insufficient evidence that GLP-1 RAs increase the risk of aspiration in association with general anesthesia or deep sedation. However, given that GLP-1 RAs may cause a delay in gastric emptying leading to retention of gastric contents, there is a theoretical risk of aspiration in patients undergoing operative procedures under general anesthesia or deep sedation. Aspiration in association with general anesthesia or deep sedation is potentially serious as it may result in severe complications.	Patients should be informed of the risk of aspiration in association with general anesthesia or deep sedation, and inform their doctor that they are taking a GLP-1 RA when undergoing planned general anesthesia or deep sedation. Doctors should follow local anesthesiologic guidelines on preoperative management of patients treated with GLP-1 RAs when possible. If anesthesia-related aspiration is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RAs. In the completed phase 3 studies with semaglutide s.c. and oral semaglutide, both the event rate and the proportion of participants experiencing confirmed pancreatitis were similar with semaglutide and comparator. Few events were confirmed; the events occurred throughout the study periods and the overall rates were similar to the rates reported in background populations.	Participants should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, semaglutide should be discontinued. If confirmed, semaglutide should not be restarted.
Neoplasms (malignant and non-malignant)	There is no evidence from clinical studies that GLP-1-based therapies increase the risk of neoplasms. However, in the semaglutide s.c. as well as oral semaglutide phase 3a studies, the proportion of participants with neoplasms (malignant and non-malignant) were slightly higher with semaglutide than with comparator. The number of participants exposed to semaglutide s.c. or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms.	Participants with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this study. Basal or squamous cell skin cancer, low-risk prostate cancer, or in situ carcinomas of the cervix or carcinoma in situ/high grade prostatic intraepithelial neoplasia (PIN) are allowed.
Intestinal obstruction	There have been post-marketing cases of intestinal obstruction reported with semaglutide. Intestinal obstruction is a severe form of constipation with blocked passage of food, liquid and stool with additional symptoms such as stomach-ache, bloating, vomiting etc. In serious cases, intestinal obstruction can lead to bowel ischemia and perforation.	Please refer to mitigations of gastrointestinal adverse events. Furthermore, participants should be informed of the characteristic symptoms of intestinal obstruction. If intestinal obstruction is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Pancreatic cancer	There is currently no support from nonclinical studies, clinical studies, or post-marketing data that GLP-1 based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies. There is no indication of an increased relative risk in the semaglutide treatment groups vs. comparator, including placebo. The rates of event adjudication committee confirmed events of pancreatic cancer were consistently low across studies.	Participants with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this study.
Medullary thyroid cancer	Thyroid C-cell tumours were seen in mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No C-cell tumours were observed in monkeys after 52 weeks exposure up to 52-fold above the clinical plasma exposure at 14 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid, and therefore the clinical relevance of the findings is considered to be low.	To mitigate this risk, participants with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) are excluded from clinical studies with semaglutide.
Study procedures		
Lumbar puncture	This is an invasive procedure with potential post-procedural risks including headache, back discomfort, infection, bleeding at the puncture site and brainstem herniation in rare cases.	The investigators must follow local standards and practices for this procedure in order to minimize the risk of complications. This includes assessment of contraindications (increased intracranial pressure, bleeding diathesis [e.g., thrombocytopenia, prothrombin time, activated partial thromboplastin time], use of anticoagulant therapy [e.g., warfarin, direct thrombin or factor inhibitors; antiplatelet therapy is not contraindicated]) based on medical history, concomitant medications and MRI (or CT) scans. As a precaution, potential participants with a platelet count <100,000/ul will not be enrolled in this study.
Risk of COVID-19 infection in relation to participation in study	Participants may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low; however, this may vary between geographical areas. To minimize the risk as much as possible, the following measures have been taken:

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
		Cautious recruitment planning to ensure controlled enrolment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control, and at sites where health care resources are evaluated to be adequate. Physical contact between participants and site staff will be limited to the extent possible, and protective measures will be implemented according to local practice.
Other		
Pregnancy and fertility	Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women.	Semaglutide should not be used during pregnancy. Women of childbearing potential are required to use highly effective contraceptive methods when participating in this study (Appendix 4, Table 10-3). If a female participant wishes to become pregnant, or pregnancy occurs during the study, treatment with study intervention be discontinued immediately (please refer to Section 7.1.1 for details). Highly effective contraception to be utilised for at least 5 half-lives (35 days) after last dose of study intervention. The effect of semaglutide on fertility in humans is unknown.

Risk assessment has been conducted for the PDS290 (DV3326-C3) pen-injector for semaglutide s.c. in accordance with ISO 14971:2019. A study-specific device evaluation has been performed to ensure safe and accurate handling and dosing of semaglutide s.c. when using the PDS290 (DV3326-C3) pen-injector by the study partner for administration of semaglutide s.c. in participants.

All identified risks associated with using PDS290 (DV3326-C3) pen-injector for semaglutide s.c. according to the clinical procedures specified in this protocol have been reduced as far as possible and are acceptable, taking into account the current state of the art. The use of PDS290 (DV3326-C3) pen-injector for semaglutide s.c. in this study is therefore considered to be of non-significant risk.

For residual risk identified for PDS (DV3326-C3) pen-injector for semaglutide s.c. see investigator's brochure[43] or updates thereof.

2.3.2 Benefit assessment

There is a significant unmet need for treatments that can alter the trajectory of this progressive disease. Based on available evidence, treatment with semaglutide is anticipated to delay decline in cognition and function in participants with MCI or mild dementia, both of the Alzheimer's type. Treatment with semaglutide is also expected to slow progression from MCI to dementia, which could have a significant socioeconomic impact. Furthermore, participants are expected to benefit from close contact with study sites, thus ensuring disease monitoring and careful medical examinations by qualified healthcare professionals during the study. This study is furthermore designed to add important medical knowledge related to molecular processes associated with

Alzheimer's disease and may thus contribute with knowledge related to treatment, diagnosis and prevention.

2.3.3 Overall benefit-risk conclusion

The safety and tolerability of semaglutide s.c. is well established in comprehensive clinical development programmes for T2DM and obesity. Based on this extensive clinical experience, all necessary precautions are implemented in the study design and planned conduct of the study to minimise risks associated with the treatment as well as participation in the study.
Taking into account the measures taken to minimise risk and burden to participants in this study, the potential risks identified in association with semaglutide s.c. are justified by the anticipated benefits that may be afforded to participants with Alzheimer's disease.

3 Objectives and endpoints

3.1 Objectives and endpoints

Study objectives and endpoints are summarised in Table 3-1.

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To investigate the effect of semaglutide s.c. 1.0 mg once-weekly versus placebo on central and peripheral inflammation in participants with Alzheimer's disease	*Co-primary:*		
	Change in gene expression assessed by scRNAseq (cells in CSF)	From baseline (week 0) to visit 5 (week 12)	Number of differentially expressed genes
	Change in gene expression assessed by scRNAseq (cells in blood)	From baseline (week 0) to visit 5 (week 12)	Number of differentially expressed genes
Secondary	**Title**	**Time frame**	**Unit**
To compare the effects of semaglutide s.c. 1.0 mg once-weekly versus placebo on safety and tolerability in participants with Alzheimer's disease	*Supportive secondary:*		
	Number of treatment emergent adverse events (TEAEs)	From baseline (week 0) to visit 5 (week 12)	Number of events
To evaluate the effects of semaglutide s.c. 1.0 mg once-weekly on safety and tolerability in participants with Alzheimer's disease	Number of treatment emergent adverse events (TEAEs)	From baseline (week 0) to end of treatment (week 64)	Number of events
To evaluate the steady state pharmacokinetics of semaglutide s.c. 1.0 mg once-weekly in participants with Alzheimer's disease	Weekly average semaglutide concentration (C_{avg}) based on population PK analysis	From visit 3 (week 4) to end of treatment (week 64)	nmol/L
Exploratory	**Title**	**Time frame**	**Unit**
To explore the effect of semaglutide s.c. 1.0 mg once-weekly versus placebo on neuroinflammatory and neurodegenerative biomarkers in participants with Alzheimer's disease	*Exploratory:*		
	Change in biofluid-based (blood or CSF) neuroinflammatory and neurodegenerative biomarkers[a]	From baseline (week 0) to visit 5 (week 12)	-
To compare the effects of semaglutide s.c. 1.0 mg once-weekly versus placebo on the proteomic profiles in CSF and plasma in participants with Alzheimer's disease	Changes in proteome in CSF	From baseline (week 0) to visit 5 (week 12)	NPX, Normalized Protein eXpression
	Changes in proteome in plasma	From baseline (week 0) to visit 5 (week 12)	NPX, Normalized Protein eXpression
To compare the effects of semaglutide s.c. 1.0 mg once-weekly versus placebo on the T cell receptor profiles in CSF and plasma in participants with Alzheimer's disease	Changes in T cell clonal landscape assessed by scTCRseq (cells in CSF)	From baseline (week 0) to visit 5 (week 12)	Morisita-Horn index
	Changes in T cell clonal landscape assessed by scTCRseq (cells in blood)	From baseline (week 0) to visit 5 (week 12)	Morisita-Horn index

Objectives	Endpoints		
To measure semaglutide concentration in the CSF in participants with Alzheimer's disease	Semaglutide concentration in CSF[b]	At week 12	-

Notes: [a] Biomarkers will be defined in the Statistical Analysis Plan (SAP) depending on the availability of validated biomarkers before database lock (DBL). Analysis will be performed only if a validated reliable assay is available at the end of study. [b] Analysis will be performed only if a validated reliable assay is available at the end of study.

Abbreviations: C_{avg} = average concentration; CSF = cerebrospinal fluid; PK = pharmacokinetics; s.c. = subcutaneous; scRNAseq = single-cell ribonucleic acid sequencing; scTCRseq = single-cell T cell receptor sequencing.

4 Study design

4.1 Overall design

This is an interventional, randomised, parallel-group, double-blind, placebo-controlled, multi-centre, multi-national study designed to evaluate the effects of semaglutide 1.0 mg versus placebo (randomised 1:1), both administered s.c. once-weekly and added to standard of care, on central and peripheral inflammation in participants with MCI or mild dementia of the Alzheimer's type.

Assessments will be performed as described in the flowchart (Section 1.2). Participants are expected to stay in the study for the complete duration of the study. Hence, participants will be followed for the complete duration of the study irrespective of their adherence to randomised study intervention or adherence to the protocol in general. Extensive efforts must be made to keep the participants on study intervention (see details in Section 7). However, in case of a potential safety concern, unacceptable intolerability or at the request of the participant, the study intervention may be discontinued. Participants should be encouraged to stay in the study irrespective of the degree of adherence to randomised treatment (investigational medical product). Furthermore, diligent, and extensive efforts should be made to collect outcome data on all randomised participants including those who discontinued treatment early.

The study consists of the following periods:

- Screening period: up to 8 weeks
- Study intervention periods
    - *Study intervention period 1* (double-blind): 12 weeks
    - *Study intervention period 2* (open-label): 52 weeks
- Follow-up period: 5 weeks

Study intervention period 1 (double-blind)

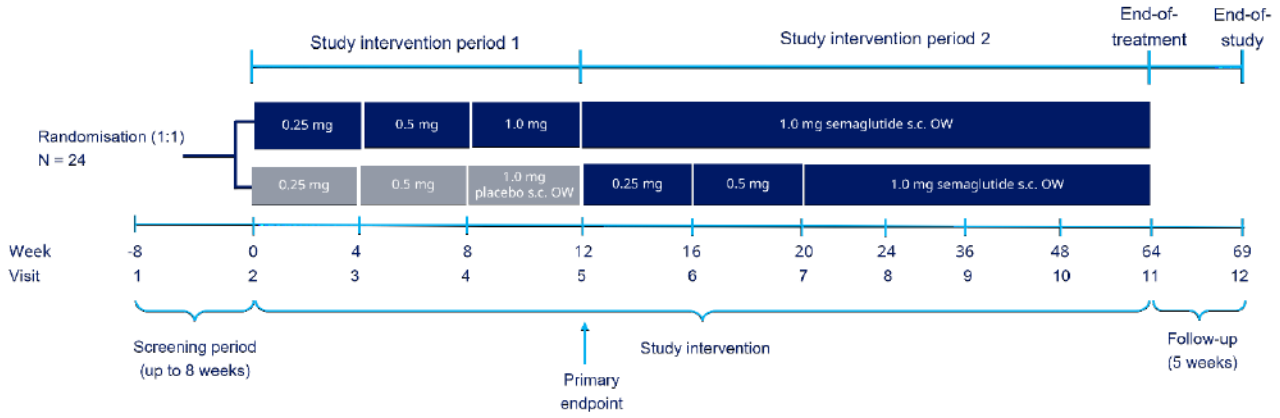
During *study intervention period 1* (from visit 2-5), a total of 24 participants will be randomised in a 1:1 manner to receive either semaglutide or placebo, both administered s.c. once-weekly as add-on therapy to standard of care. *Study intervention period 1* comprises an 8-week dose escalation period with dose escalation every 4 weeks followed by a 4-week maintenance period.

Study intervention period 2 (open-label)

During *study intervention period 2* (from visit 5-11), all participants will receive semaglutide s.c. 1.0 mg once weekly in an open-label manner. Participants randomised to placebo during *study intervention period 1* will enter a new 8-week dose escalation period with dose escalation every 4 weeks followed by a 44-week maintenance period. Participants randomised to semaglutide s.c. 1.0 mg during *study intervention period 1* will remain on the 1.0 mg target maintenance dose during *study intervention period 2* for a 52-week maintenance period.

The planned study duration for the individual participant will be up to 77 weeks (including screening period). A schematic overview of the study is provided in Figure 4-1 below.

Figure 4-1 Study design



Abbreviations: N = number of participants; OW = once-weekly; s.c. = subcutaneous.

4.2 Scientific rationale for study design

A duration of 12 weeks for *study intervention period 1* is selected to allow sufficient time to observe a meaningful change in gene expression of central and peripheral inflammatory cells. To understand the mechanism of action of semaglutide in Alzheimer's disease, a global database lock (DBL) will be performed, and endpoints will be assessed at the end of *study intervention period 1*. During *study intervention period 2*, all participants will continue treatment with semaglutide s.c. once weekly in an open-label manner for an additional 52 weeks. Participants initially randomised to semaglutide will remain on the target maintenance dose of 1.0 mg once-weekly for 52 weeks without re-escalation; participants initially randomised to placebo will enter a new 8-week dose escalation period with dose escalation every 4 weeks followed by a 44-week maintenance period. Blood samples collected during *study intervention period 2* will determine the pharmacokinetic response for semaglutide s.c. formulation and to determine the safety and tolerability in participants. A follow-up period of 5 weeks, after completion of 64-week treatment, is planned to allow complete wash-out of semaglutide. Investigators and participants will remain blinded to treatment allocation throughout the randomised part of the study.

The dose of semaglutide s.c. will be escalated in 4-weeks intervals aligned with the T2DM development program (SUSTAIN) in order to lower the occurrence of gastrointestinal AEs. Dose escalation of semaglutide/placebo will take place during the first 8 weeks after randomisation (Figure 4-1). Participants are intended to remain on the target maintenance dose level of 1.0 mg s.c. throughout the two study intervention periods; however, to accommodate participant tolerability and safety and to ensure as much exposure as possible, dose reductions, extensions of dose-escalation intervals and treatment pauses are allowed (e.g., if treatment with the study intervention is associated with unacceptable AEs or due to other circumstances).

4.3 Justification for dose

Semaglutide s.c. 1.0 mg once weekly is selected in this exploratory study, considering its well-established safety profile and extensive safety data from the development programmes for T2DM and chronic weight management which showed no dose-dependent safety issues besides gastrointestinal AEs. Participants will be initiated at a once weekly dose of 0.25 mg and follow a

fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5 mg/week and 1.0 mg/week), until the target maintenance dose of 1.0 mg is reached after 8 weeks.

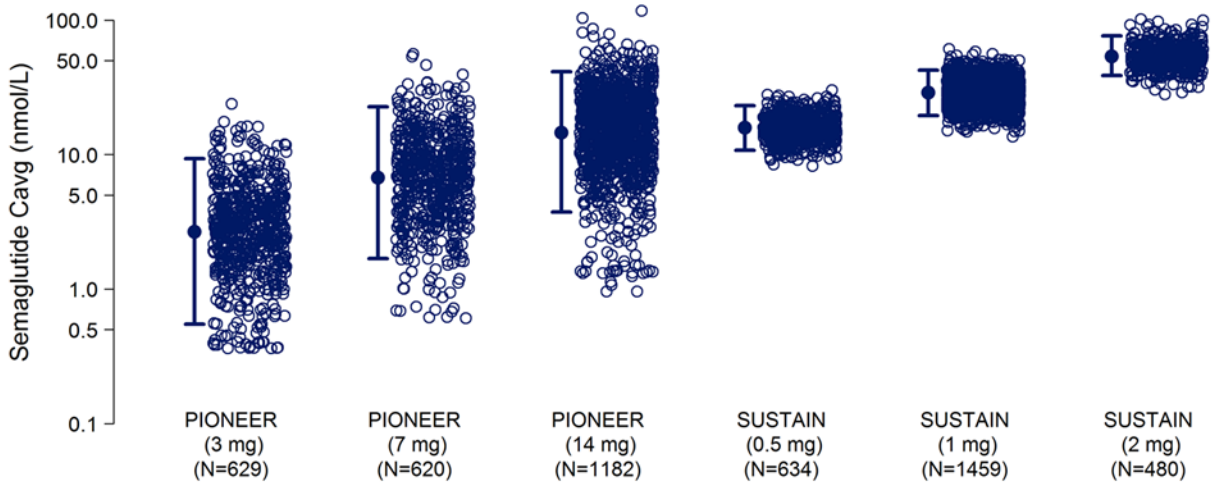
The clinical evidence on the reduced risk of dementia is based on real-world data in which the majority of patients received liraglutide treatment and were expected to be on the approved doses for treatment of T2DM i.e., 1.2 or 1.8 mg. Reduced risk of dementia was also observed in a post-hoc analysis using pooled data from large randomised controlled studies where patients were exposed to liraglutide up to 1.8 mg, semaglutide s.c. 0.5 or 1.0 mg or oral semaglutide up to 14 mg (LEADER, SUSTAIN 6 and PIONEER 6).[37]

Similar PK properties and exposure-response across different routes of administration of semaglutide have been demonstrated. The clinical efficacy and safety data obtained in the two large clinical development programs in T2DM for oral semaglutide once-daily (PIONEER) and semaglutide s.c. once-weekly (SUSTAIN) support that the systemic effects of semaglutide are independent of route of administration and demonstrate consistent effects on CRP, glycemic control and body weight.[44] Hence, once semaglutide has entered the systemic circulation, the properties and actions of the molecule are well known.

Additionally, model-derived steady-state exposures, estimated based on sparse PK sampling from PIONEER and SUSTAIN, showed that the range of exposure was smaller following treatment with semaglutide s.c. compared to oral semaglutide (~ 1% bioavailability) due to the higher variability in exposure following administration of oral semaglutide (Figure 4-2 and Table 4-1). Semaglutide s.c. 1.0 mg once-weekly is the lowest s.c. dose fully contained within the upper limit of the 90% exposure range of the study intervention evaluated in the ongoing evoke^{+}/evoke studies (oral semaglutide 14 mg) (Table 4-1). [redacted]

Importantly, exposure associated with the 1.0 mg dose of semaglutide s.c. was safe and well-tolerated across the development programme for T2DM (SUSTAIN). The studies included a broad population of patients with T2DM including vulnerable patients i.e., those at high risk of or having established cardiovascular disease and patients with renal or hepatic impairment. Furthermore, based on the clinical pharmacology programme, no dose adjustments are required for patients according to age, renal impairment, or hepatic impairment.

Figure 4-2 Semaglutide exposures with oral semaglutide and semaglutide s.c.



Notes: Data are individual C_{avg} values (open symbols) and geometric means with 90% ranges (closed symbols with vertical bars). Data from PIONEER 1, 2, 3, 5, 8, and 9 (oral semaglutide); SUSTAIN 1, 2, 3 and 6, SUSTAIN FORTE and SUSTAIN Japan OAD (s.c. semaglutide).

Abbreviations: C_{avg} = average concentration; OAD = oral anti-diabetic drug; s.c. = subcutaneous.

Table 4-1 Oral semaglutide exposures compared to semaglutide s.c. in phase 3a studies

Dose	Number of participants	C_{avg} (nmol/L)			
		Geometric mean	median	range	90% range
0.5 mg s.c.	556	15.9	16.1	8.3-30.2	10.8-23.1
1.0 mg s.c.	867	29.7	29.9	14.8-61.3	**20.3-43.6**
2.0 mg s.c.	480	54	53	28-102	39-76
3 mg oral	629	2.7	2.9	0.4-23.9	0.5-9.3
7 mg oral	620	6.7	7.1	0.6-56.2	1.7-22.7
14 mg oral	1182	14.6	15.7	1.0-117.9	**3.7-41.3**

Notes: Data based on individual parameter estimates from population PK modelling of SUSTAIN 1, 2, 3, 6, SUSTAIN-Japan (and 2.0 mg data from SUSTAIN FORTE) and PIONEER 1, 2, 3, 5, 8, and 9.

Abbreviation: C_{avg} = average concentration; PK = pharmacokinetics.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study globally.

A participant is considered to have completed the study if he/she has:

- completed all periods of the study including the last visit (follow-up visit – visit 12) *or*
- if a randomised participant has died during study, 'date of study completion' is the date of death.

The primary endpoint is evaluated at visit 5 (week 12). The primary completion date (PCD) is defined as the date of visit 5 (week 12) on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is withdrawn early, the PCD is considered the date when the last participant would have completed visit 5.

5 Study population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Pre-screening is defined as review of the participant medical records, including handing out participant information, as well as database review. Any pre-screening activities must be documented on site by the investigator.

Local requirement may apply, see country-specific requirements (Appendix 8, Section 10.8).

5.1 Inclusion criteria

All inclusion criteria are based on the participants' medical records, except for inclusion criteria #4 (BMI assessed at screening), #6 (CDR global score assessed at screening), and #7 (amyloid positivity established at special laboratory) assessed at screening (visit 1).

Local requirements may apply. Denmark, Sweden, and Switzerland: see country-specific requirements (Appendix 8, Section 10.8).

Participants are eligible to be included in the study only if all the following criteria apply:
General

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male or female.
3. Age 55-75 years (both inclusive) at the time of signing the informed consent.
4. Body mass index (BMI) ≥18.5 kg/m^2 and <30.0 kg/m^2 at screening (visit 1).

Disease-specific

5. MCI or mild dementia of the Alzheimer's type according to the NIA-AA 2018 criteria.
6. CDR global score of 0.5 or 1 at screening (visit 1).
7. Amyloid positivity established with either historical amyloid PET *or* historical CSF $A\beta_{1-42}$ *or* historical CSF $A\beta_{1-42}/A\beta_{1-40}$ (historical data within the last 5 years) *or* blood sample for amyloid biomarker ($A\beta_{42}/A\beta_{40}$ ratio and p-tau_{217}/np-tau_{217} ratio) at screening (visit 1).
   For definition of amyloid positivity, see Section 8.1.2
8. Treated with acetylcholinesterase inhibitors (approved for the treatment of Alzheimer's disease) and on stable dose for > 90 days before screening (visit 1).
9. Have a competent study partner who is a partner/informant with a close relationship to the participant and willing to consent to attend clinic visits (that require informant input for CDR scale) with the participant and to participate throughout the duration of the study. The study partner needs to spend time with the participant at least 4 times a week (totalling a minimum of 10 hours per week), in order to be able to provide adequate information needed for the study. Additionally, the study partner must be willing to inject the participant with study intervention once-weekly.
10. Participant and study partner must be able to read, write and fluently speak the language in which the tests are administered with sufficient proficiency.

5.2 Exclusion criteria

All exclusion criteria are based on the participants' medical records, except for exclusion criteria #17 and #18 (brain MRI scan assessed by local read), #10 to #16 (central laboratory tests) assessed at screening (visit 1).

Local requirements may apply. Denmark: see country-specific requirements (Appendix 8, Section 10.8).

Participants are excluded from the study if any of the following criteria apply:

General

1. Known or suspected hypersensitivity to study intervention or related products.
2. Previous randomisation in this study.
3. More than one rescreening for this study.
4. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using adequate contraceptive method, as defined in Appendix 4 (Section 10.4).
5. Participation (i.e., signed informed consent) in any other interventional clinical study within 90 days before screening (visit 1). *(Note: Participants who screen fail in the evoke or evoke+ study is not exclusionary, and potential participants may be screened for this study, at the discretion of the investigator. For details, see Section 5.4.2).*
6. Participation in any disease modifying interventional clinical study in Alzheimer's disease within the last 6 months before screening (visit 1) unless documentation of receipt of placebo is available. *(Note: Participants who screen fail in the evoke or evoke+ study is not exclusionary, and potential participants may be screened for this study, at the discretion of the investigator. For details, see Section 5.4.2).*
7. History of participation in any Aβ- or tau-reducing clinical study (small molecules or biologics or active vaccines), unless documentation of receipt of placebo is available.
8. Any contraindication to having a lumbar puncture, e.g., due to lumbar spine deformity or low platelet count below 100,000/ul, or a bleeding disorder.
9. Any disorder which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.

Laboratory values

10. Impaired liver function defined as ALT ≥ 2.5 times or bilirubin >1.5 times upper normal limit at screening (visit 1).
11. Diagnostic test results positive for hepatitis B or hepatitis C infection at screening (visit 1).
12. Diagnostic test results positive for HIV-1 or HIV-2 infection at screening (visit 1).
13. Renal impairment defined as eGFR < 30 mL/min/1.73m^2 (CKD-EPI[15]) at screening (visit 1).
14. Platelet count <100,000/ul at screening (visit 1).
15. Prothrombin time INR more than >1.1 and activated partial thromboplastin time more than normal (visit 1).
16. Clinically significant abnormalities in thyroid function, or clinically significant vitamin B12 or folate deficiency at screening (visit 1) as determined by the investigator (participants with adequately treated thyroid disease [excluding medullary thyroid carcinoma] are eligible).

Medical conditions - neurological/psychiatric disorder

17. Brain MRI scan suggestive of clinically significant structural CNS disease confirmed by local read (e.g., cerebral large-vessel disease [large vessel (cortical) infarcts >10 mm in diameter], prior macro-haemorrhage [>1 cm^3], cerebral vascular malformations, cortical hemosiderosis,

intracranial aneurism(s), intracranial tumours, changes suggestive of normal pressure hydrocephalus).

18. Brain MRI scan suggestive of significant small vessel pathology confirmed by local read and defined as >1 lacunar infarct and/or white matter hyperintensity (WMH) Fazekas[14] scale >2, (WM >20 mm) in the deep white matter and periventricular regions.
19. Amyloid negative based on amyloid PET scan or CSF Aβ test within the last 2 years before the day of screening (visit 1). In case both CSF $A\beta_{1-42}$ and $A\beta_{1-40}$ were measured, the test is only considered negative if both $A\beta_{1-42}$ and the $A\beta_{1-42}/A\beta_{1-40}$ ratio were negative based on respective cut-offs.
20. Evidence of a relevant neurological disorder other than Alzheimer's disease at screening (visit 1), including but not limited to Parkinson's disease, Lewy body disease, frontotemporal dementia of any type, progressive supranuclear palsy, neurosyphilis, cortico-basal degeneration, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, systemic lupus erythematosus, infection of the central nervous system or spinal roots, intellectual disability, hypoxic cerebral damage, or significant head trauma with loss of consciousness that led to persistent cognitive deficits.
21. Evidence of a clinically relevant psychiatric disorder, based on Diagnostic and Statistical Manual of Mental Disorders (DSM–5) criteria, including schizophrenia or other psychotic disorder, or bipolar disorder. A participant with a history of major depression who has not had an episode in the last 24 months before the day of screening (visit 1) and is considered in remission or who´s depression is controlled with treatment can be included in the study per investigator's judgement.
22. Imminent risk of self-harm, based on clinical interview and responses on the Columbia Suicide Severity Rating Scale (C-SSRS), or of harm to self or others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (e.g., positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) in the past 2 months or suicidal behaviour in the past 6 months before the day of screening (visit 1).

Medical conditions – infections/immunosuppression

23. Clinical evidence of, or suspicion of, infection (e.g., pneumonia, urinary tract infection) within the 4 weeks prior to randomisation (visit 2) at the discretion of the investigator.
24. History of recurrent serious infections leading to hospitalisation in the 12 months prior to randomisation (visit 2).
25. History of infection of the brain or spinal cord, or spinal roots in the 12 months prior to randomisation (visit 2).
26. History or evidence of autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, lupus, glomerulonephritis, psoriasis (but not limited to):
    - Any other medical condition that would require use of systemic corticosteroids or immunosuppressants or immunostimulants in the 12 months prior to screening (visit 1).

Medical conditions – general health and safety

27. History of alcoholism or drug dependency/abuse within the last 5 years before the day of screening (visit 1).
28. Diagnosed with type 1 or type 2 diabetes mellitus.
29. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.

30. Presence or history of malignant neoplasms or in situ carcinomas (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, high grade prostatic intraepithelial neoplasia (PIN), low-risk prostate cancer[a] or in situ prostate cancer) within 5 years before screening (visit 1).
31. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 90 days prior to the day of screening (visit 1).
32. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening (visit 1).
33. Major cardiac surgical, non-cardiac surgical, or major endoscopic procedure (thoracoscopic or laparoscopic) within the past 60 days prior to screening (visit 1) or any major surgical procedure planned at the time of randomisation (visit 2).

Prior or current medication

34. Current or previous treatment with any GLP-1 RA within 90 days prior to the day of screening (visit 1).
35. Use of the following prohibited medication related to the nervous system:

Table 5-1 Prohibited medication related to central nervous system

a)	Anti-amyloid active vaccines (ever received).
b)	Anticholinergic medications of moderate or greater potency[a] used regularly (> 2 doses/week) within 4 weeks of screening. *Exceptions: Daily use of anticholinergic medications for incontinence (darifenacin, solifenacin, fesoterodine, trospium), nasal spray for rhinorrhoea (e.g., ipratropium) or inhalants for pulmonary disorders (tiotropium) provided stable dose for 4 weeks prior to screening.*
c)	Anti-parkinsonian medications within 3 months of screening. *Exceptions: Dopamine agonists pramipexole or ropinirole for treating restless leg syndrome provided stable dose for 3 months prior to screening.*
d)	Anticonvulsants within 3 months of screening. *Exceptions: Pregabalin or gabapentin for neuropathic pain provided stable dose for 4 weeks prior to screening.*
e)	Neuroleptics within 3 months of screening.
f)	Antidepressants with anticholinergic properties of moderate or greater potency[a] within 4 weeks of screening (antidepressants of low anticholinergic potency are allowed provided a stable dose for 4 weeks prior to screening).
g)	Benzodiazepines and sedatives used regularly (> 2 doses/week) within 4 weeks of screening. *Exceptions: Daily use of the following medications for sleep provided stable dose for 4 weeks prior to screening:* • zaleplon ≤ 5 mg, zopiclone ≤7.5 mg, eszopiclone ≤ 3 mg, zolpidem ≤ 5 mg • trazodone, suvorexant, or mirtazapine
h)	Morphine and narcotic analgesics within 3 months of screening. A short use (<5 days) in relation to surgery or acute injury >4 weeks before screening is not exclusionary.
i)	Stimulant medications (e.g., amphetamine, methylphenidate, atomoxetine, modafinil) within 4 weeks of screening.
j)	Medical marijuana, cannabis and cannabidiol (CBD)
k)	Any anti amyloid-beta or anti-tau drugs (ever received).
l)	Any Alzheimer's disease modifying treatment within the last 6 months
m)	Memantine, unless on a stable dose > 3 months before screening

[a] The anticholinergic potency can be assessed as described in Salahudeen et al. 2015.[45]

36. Received a vaccine product (including booster) 4 weeks prior to screening (visit 1) or expected to receive a vaccine product (including booster) before visit 5.
37. Use of any systemic immunomodulating drugs (small molecules and/or biologics) in the last 12 months prior to screening (visit 1) or anticipated use of such drugs during *study intervention*

[a] Criteria for low-risk prostate cancer are: prostate-specific antigen (PSA) lower than 10, Gleason score 6 (3+3), and clinical stage (palpatory stage) cT1c-cT2a.

period 1 (i.e., during the first 12 weeks of treatment until visit 5), such as corticosteroids for systemic use, immunostimulants and immunosuppressants.

38. Use of anti-neoplastic (cancer) drugs in the last 12 months prior to screening (visit 1) or anticipated use of such drugs during *study intervention period 1* (i.e., during the first 12 weeks of treatment until visit 5).

5.3 Lifestyle considerations

There are no restrictions to lifestyle in the study.

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently eligible for participation according to the inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, results of laboratory analyses (e.g., amyloid positivity, if available), and any serious adverse event (SAE).

A screen failure must be registered in the RTSM. If participants withdraw their consent prior to randomisation or do not return for randomisation a screen failure must be registered in the RTSM. The reason for failure will in all cases be captured in the electronic case report form (eCRF).

Individuals who do not meet the criteria for participation in this study may be rescreened (Section 5.4.1). Individuals who are rescreened are required to sign a new informed consent form and provided with a new subject ID. Rescreening must be registered in the RTSM.

5.4.1 Rescreening criteria

Rescreening is allowed for the following criteria:

- Inclusion criterion: #8.
- Exclusion criteria: #23 to #25, #30, #31, #33 to #38.

Rescreening should only be performed if the investigator considers it likely the participant would be eligible based on the new screening.

A new subject ID must be assigned in the RTSM.

In case of technical issues (e.g., haemolysed or lost samples), re-sampling is allowed for the affected laboratory parameters and is not considered rescreening.

For rescreening, the following data obtained as part of this protocol is acceptable and does not need to be repeated:

- Results of the CDR assessment can be reused if ≤ 6 weeks old from the day the scale was administered.
- Brain MRI scan should not be repeated if ≤ 3 months old.

5.4.2 Screening of potential participants who screen fail in the evoke or evoke+ study

The following recommendations are applicable only for study sites conducting all of the following studies: NN6535-4725 (evoke+), NN6535-4730 (evoke), and NN6535-7519.

Participants who are screen failures in evoke+ (NN6535-4725) or evoke (NN6535-4730) should not be screened for study NN6535-7519, unless amyloid positivity was already established using historical data (amyloid PET or CSF Aβ1-42 or CSF Aβ1-42/Aβ1-40 assays) and the screen failure was due to one of the following reasons:

- Participant did not meet inclusion criterion related to MMSE ≥22.
- Participant did not meet inclusion criterion related to RBANS delayed memory index score of ≤85.
- CDR global score of 0.5 and CDR score of 0 in all three instrumental activities of daily living categories (personal care, home & hobbies, community affairs).

The screening procedure described in Figure 8-1 must be performed for these participants with the following considerations:

- Brain MRI scans should not be repeated but instead submitted for local reading if ≤ 3 months old from the day imaging was performed.

5.5 Run-in criteria and/or randomisation criteria and/or dosing day criteria

Potential participants must be eligible for the study based on the in- and exclusion criteria (Sections 5.1 and 5.2) prior to randomisation. First dose of study intervention must only be administered after all baseline assessment are completed at visit 2.

5.6 Assessment of eligibility

It is the responsibility of the investigator to have sufficient evidence to ensure eligibility. If a potential participant is not from the investigators practice, reasonable efforts must be made to obtain a copy of the medical records for a potential participant from relevant party e.g., the primary physician and hospitals. It is at the investigator's discretion on a case-by-case basis to decide if the complete medical records are needed or if the available documentation is enough to determine whether a potential participant is eligible. The values used to assess eligibility must reflect the current health status of the potential participant.

Potential participants who do not fully meet eligibility (inclusion/exclusion) criteria must not be randomised. If a potential participant is randomised in error this will be handled as an important protocol deviation and the IRB/IEC and regulatory authorities must be notified according to local requirements. If there are no safety concerns, treatment with study intervention can be continued or resumed at the discretion of the investigator after a discussion with a Novo Nordisk medical expert.

Local requirements may apply, see country-specific requirements (Appendix 8, Section 10.8).

6 Study interventions and concomitant therapy

6.1 Study interventions administered

Study intervention is defined as all pre-specified investigational and auxiliary medicinal products, medical devices and other intervention(s) (e.g., surgical and behavioural), intended to be administered to the study participants during the study conduct according to the study protocol.

Investigational interventions are a subset of study interventions that are being tested or used as a control (e.g., placebo or active control).

The term 'trial product' is used in the protocol when referring to specific actions to be taken (e.g., actions related to shipping and storage), that only apply for these products. In this study, 'trial products' comprise investigational medicinal products (IMPs).

The term 'study intervention' is used throughout the protocol to describe the intervention including the trial product.

Local requirements may apply. Sweden: see country-specific requirements (Appendix 8, Section 10.8)

6.1.1 Investigational medicinal products (IMP)

The IMPs (study intervention) provided by Novo Nordisk are listed in Table 6-1. The study interventions are packed blinded and are visually identical. The doses to be administered in each study arm during the dose escalation steps and the maintenance periods of the double-blind (*study intervention period 1*) and open-label (*study intervention period 2*) part of the study are presented in Table 6-2 and Table 6-3, respectively.

Table 6-1 Study interventions provided by Novo Nordisk

Intervention arm	Semaglutide 1.0 mg	Semaglutide placebo
Intervention name	Semaglutide B	Semaglutide placebo
Intervention type	IMP, test product	IMP, reference therapy
Pharmaceutical form	Solution for injection	
Route of administration	Subcutaneous	
Trial product strength	1.34 mg/mL	Placebo
Dose and dose frequency	Dosing is once weekly with dose increases every 4 weeks, until the target maintenance dose of 1.0 mg/week is reached after 8 weeks. Please refer to Section 6.1.3 for further details on dose escalation and maintenance.	
Dosing instructions and administration	Injection once weekly at the same time of the week (to the extent possible). Injections could be administered in the thigh, abdomen, or upper arm, and at any time of the day irrespective of meals. For information on missed dose, see Section 6.1.2.	
Sourcing	Manufactured and supplied by Novo Nordisk A/S	
Packaging and labelling	• Labelled and packaged by Novo Nordisk A/S. • Labelled in accordance with EU CTR Annex VI,[46] local regulations and study requirements. • Study intervention is provided in 1.5 mL pre-filled PDS290 (DV3326-C3) pen-injector (device constituent of non-approved device combination product[a]). The device constituent is not under investigation.	

Notes: [a] The drug-device combination product is used outside its approved intended use. See Section 2.3.1 for information on study-specific device risk assessment.

Abbreviations: IMP, investigational medicinal product.

6.1.2 Administration of study intervention

All baseline assessments must be done prior to administration of the first dose of study intervention.

Only participants enrolled in the study may use study intervention.

Study partners will be trained and instructed to inject the participants with study intervention once-weekly. The injection can be administered at any time of the day irrespective of meals, but on the same day of the week.

If a single dose is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is more than 2 days (>48 hours). If a dose is missed and the next scheduled dose is less than 2 days (<48 hours) away, the study partner should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week. If 2 or more consecutive doses of study intervention are missed, the participant should be encouraged to re-commence the treatment if considered safe as per the investigator's discretion and if the participant does not meet any of the discontinuation criteria (Section 7.1). Study intervention should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of study intervention is at the investigator's discretion. In case of questions related to re-initiation of study intervention, the investigator should consult Novo Nordisk global medical expert.

Information about the pre-filled PDS290 pen-injector may be found in the investigator's brochure[43] and any updates hereof.

Information regarding the use of the pre-filled PDS290 pen-injector is available in the Directions for use (DFU) document. Injections are to be performed s.c. in the thigh, abdomen, or upper arm.

Training in DFU is the responsibility of the investigator or a delegate. The investigator must document that DFU was given to the participant and study partner verbally and in writing as a DFU document at the first dispensing visit (as specified in the flowchart) and thereafter as needed during the study (Section 1.2). Moreover, the study partner must be trained in handling the injection when dispensed to the participant the first time and thereafter as indicated in the flowchart (Section 1.2) and as needed during the study in order to ensure correct study intervention administration. Furthermore, the initial administration of study intervention is to be performed by the study partner during the study visit, as indicated in the flowchart (Section 1.2), and the study partner should be observed by the investigator for correct administration of study intervention.

6.1.3 Dose escalation

Dose escalation of semaglutide/semaglutide placebo should take place during the first 8 weeks of *study intervention period 1* after randomisation as described in Table 6-2. All participants should aim at reaching the target maintenance dose of 1.0 mg semaglutide once-weekly or the corresponding volume of placebo. During *study intervention period 2*, participants initially randomised to semaglutide will remain on the target maintenance dose of 1.0 mg once weekly for 52 weeks without re-escalation. Participants initially randomised to placebo will enter a new dose escalation period of 8 weeks (starting with semaglutide s.c. 0.25 mg once-weekly for 4 weeks followed by 0.5 mg for 4 weeks before moving to the target maintenance dose of 1.0 mg) as described in Table 6-3.

[redacted] This should only be allowed if the participant otherwise will discontinue study intervention completely and if considered safe to continue study intervention, as per the investigator's discretion. It is recommended that the participant makes at least one attempt to re-escalate to the target maintenance dose of 1.0 mg once-weekly, as per the investigator's discretion.

It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.

Table 6-2 Dose escalation and maintenance of semaglutide 1.0 mg once-weekly/semaglutide placebo during study intervention period 1 (double-blind)

Intervention arm	Dose	Value shown in dose counter	Duration
Dose escalation period			
Semaglutide B 1.34 mg/mL PDS290/semaglutide placebo	0.25 mg	0.25	4 weeks
Semaglutide B 1.34 mg/mL PDS290/semaglutide placebo	0.5 mg	0.5	4 weeks
Maintenance period			

Intervention arm	Dose	Value shown in dose counter	Duration
Semaglutide B 1.34 mg/mL PDS290/semaglutide placebo	1.0 mg	1	4 weeks

Table 6-3 Dose escalation and maintenance of semaglutide 1.0 mg once-weekly during study intervention period 2 (open-label)

Intervention arm	Dose	Value shown in dose counter	Duration
Dose escalation period[a]			
Semaglutide B 1.34 mg/mL PDS290	0.25 mg	0.25	4 weeks
Semaglutide B 1.34 mg/mL PDS290	0.5 mg	0.5	4 weeks
Maintenance period			
Semaglutide B 1.34 mg/mL PDS290	1.0 mg	1	44 weeks

Note: [a] During *study intervention period 2*, participants initially randomised to semaglutide will remain on the target maintenance dose of 1.0 mg once weekly for 52 weeks without re-escalation.

6.1.4 Other study supplies including non-investigational medical device

The following auxiliary supplies will be provided by Novo Nordisk in accordance with the Trial Materials Manual (TMM) (see Table 6-4).

Table 6-4 Study auxiliary supplies provided by Novo Nordisk

Auxiliary supply	Details
Needles	• Needles for PDS290 pen-injector: Disposable NovoFine® Plus 32G 4 mm pen needles to be attached before injection. Details are provided in the TMM. • Only needles provided and approved by Novo Nordisk must be used for administration of study intervention.
Directions for use (DFU)	• DFU for the 1.5 mL pre-filled PDS290 pen-injector.

The PDS290 (DV3326-C3) pen-injector (device constituent) is used for administration of study intervention and is a pre-filled pen-injector which is not under investigation in this study. The PDS290 pen-injector is a pre-filled, multi-dose, disposable pen-injector containing a 1.5 mL cartridge with either semaglutide 1.34 mg/mL or placebo solution. The PDS290 (DV3326-C3) is designed to deliver once weekly s.c. injection of 0.25 mg, 0.5 mg and 1.0 mg semaglutide 1.34 mg/mL or placebo. The intended doses are displayed in the dose counter window in milligrams.

6.2 Preparation, handling, storage and accountability

6.2.1 Dispensing of study intervention administration

Each study site will be supplied with sufficient study interventions for the study on an ongoing basis according to recruitment and randomisation.

Only participants enrolled in the study may use study intervention and only delegated site staff may supply study intervention.

The initial administration of study intervention is to be performed during study visit 2. Study intervention will be dispensed to the participant at relevant visits for the remaining treatment periods (see flowchart, Section 1.2).

If a participant is unable to attend the site for a dispensing visit (see flowchart in Section 1.2), a non-participating person (e.g., the study partner) may, however, collect the allocated study intervention on behalf of the participant. If study intervention is collected by a non-participant, this must be agreed with the participant beforehand and thoroughly documented at the site e.g., by means of a letter of authorisation issued by the participant, and, on each occasion, the investigator must follow up by contacting the participant.

6.2.2 Preparation of study intervention

The study intervention is provided in a ready-to-use pre-filled pen-injector, i.e., no preparation is needed. Conditions for storage outside the refrigerator will be available on the label and in the TMM. For details regarding administration of study intervention, please refer to Section 6.1.2.

6.2.3 Handling and storage of study intervention

Acceptable temperature ranges and conditions for storage and handling of each study intervention in- and outside the refrigerator are described in the TMM. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study interventions received, and that any discrepancies are reported and resolved before use of the study intervention.

All study intervention must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff. Product storage conditions will be available on the label and in the TMM.

The investigator must inform Novo Nordisk immediately if any study intervention has been stored outside specified conditions. The study intervention must not be dispensed to any participant before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the TMM.

The investigator or designee must instruct the participant on how to manage the time of storage of the dispensed products outside refrigerator.

6.2.4 Accountability of study intervention

The investigator or designee is responsible for study intervention accountability and record maintenance (i.e., receipt, accountability, and final disposition records). Drug accountability is performed by using the RTSM and should also be recorded in a separate study intervention accountability log.

Participants and study partners must ensure that all used, and unused study intervention including empty packaging material is returned as instructed by the investigator. The investigator or designee must instruct the participant in what to return at next visit.

Used needles are potentially hazardous materials that should be disposed of in a safe manner and therefore will not be retained for drug accountability purposes. Empty packaging will be used to perform accountability of used study intervention. Study sites will provide participants and study partners with a sharps container for disposal of used needles. Participants and study partners should return the sharps containers to the study site at each visit for disposal using appropriate biohazard precautions.

Destruction of study intervention can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor. Destruction of study intervention must be documented in the RTSM.

All returned (used or un-used), expired or damaged study intervention (for technical complaint samples, see Appendix 6 (Section 10.6)) must be stored separately from non-allocated study intervention. No temperature monitoring is required. Non-allocated study intervention, including expired or damaged products, must be accounted by the site and reconciled by the monitor, as unused, at the latest at closure of the site.

6.3 Measures to minimise bias: Randomisation and blinding

Randomisation

All participants will be screened and centrally randomised using a RTSM and assigned to the next available treatment according to randomisation schedule. Study intervention will be dispensed at the study visits summarised in the flowchart (Section 1.2).

At screening, each participant will be assigned a unique 6-digit subject ID which will remain the same throughout the study. Each site is assigned a 3-digit number and all subject IDs will start with the site number. Subject IDs must not be re-assigned.

Blinding

This is a double-blind study in which participants, study partners, care providers, and investigators are blinded to study intervention allocation. The study intervention containing the active drug and the placebo are visually identical and will be packed in a manner that maintains blinding.

RTSM is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' study intervention is warranted. The safety of the participant must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted during *study intervention period 1*, the investigator may, at the investigators' discretion, contact the sponsor to discuss the situation prior to unblinding a participants' study intervention, unless this could delay emergency treatment of the participant.

If a participants' study intervention is unblinded in RTSM, Novo Nordisk (Global Safety department) will be notified automatically via RTSM. The date and reason that the blind was broken must be recorded in the source documentation. The person breaking the blind must print the blind break confirmation notification generated by the RTSM, sign and date the document. If

RTSM is not accessible at the time of blind break, the RTSM helpdesk should be contacted. Contact details are listed in Attachment I.

The participant should continue in the study after breaking the blind. Treatment with study intervention can be resumed if there are no safety concerns at the discretion of the investigator.

When the blind is broken, the study intervention allocation will also be accessible to the investigator and the Novo Nordisk Global Safety department.

Study intervention allocation will also be accessible to the special laboratories responsible for PK (Section 8.5) and immunogenicity analyses.

6.4 Study intervention compliance

6.4.1 Drug treatment compliance

Throughout the study, the investigator will remind the participants to follow the study procedures and requirements to encourage participant compliance.

When participants self-administer trial product at home, compliance with trial product administration will be assessed, and the assessment documented in source documents at each visit where information is available.

Treatment compliance will be assessed by monitoring of drug accountability and by discussing treatment compliance and dosing conditions with the participant and study partner. Treatment compliance is defined as taking between 80%-120% of the dose as prescribed between visits, and not missing two or more consecutive doses. The investigator must assess the amount of study intervention returned, including both unused study intervention and empty packaging (as a surrogate for used study intervention), and compare to what was dispensed at the previous visit and, in case of discrepancies, question the participant and study partner.

If any suspicion of non-compliance arises, the site must enter into a dialogue with the participant, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Accountability information; counting returned trial product, visual inspection of pens
- Review of dosing diaries
- Questioning of participants and study partners

If the participant has been off treatment, continuation of study intervention should be encouraged if considered safe as per the investigator's discretion. Trial product start and stop dates will be recorded in the eCRF.

6.5 Dose modification

To mitigate gastrointestinal side effects with GLP-1 RA treatment, dose escalation to the target maintenance dose of 1.0 mg once weekly is required. Participants should follow a fixed dose-escalation regimen, starting at randomisation with initiation at a once weekly dose 0.25 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5 and 1.0

mg/week), aiming at reaching the target maintenance dose of 1.0 mg (or the corresponding volume of placebo) after 8 weeks as described in Table 6-2.

No dose modification are allowed during the study and participants should remain on the 1.0 mg dose level until the end-of-treatment visit (visit 11); however, dose reductions, extensions of dose escalation intervals and treatment pauses are allowed e.g., if treatment with study intervention is associated with unacceptable AEs or due to other circumstances (see Section 7 for details).

The date of initiation and dose of the study intervention should be recorded in the eCRF. Any change to dose including date of change or discontinuation should be recorded in the eCRF throughout the study.

If study intervention is discontinued, participants should continue to follow the study schedule without being withdrawn from the study. Treatment with study intervention should be resumed if deemed safe at the discretion of the investigator.

Please refer to Section 6.1.2 for a description of missed doses.

6.6 Continued access to study intervention after end of study

When discontinuing investigational intervention, the participant should be treated at the discretion of the treating physician.

Semaglutide will not be available for prescription for Alzheimer's disease until marketing authorisation is issued.

6.7 Treatment of overdose

Overdoses of semaglutide s.c. up to 4 mg in a single dose have been reported in clinical studies. The most commonly reported AE was nausea. All participants recovered without complications.

There is no specific antidote for overdose with semaglutide. In the event of an overdose, the investigator should closely monitor the participant for overdose-related AE/SAE and laboratory abnormalities. In the event of overdose, appropriate supportive treatment should be initiated according to the participant's clinical signs and symptoms. Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the participant. A prolonged period of observation and treatment may be necessary, considering the long half-life of semaglutide of approximately one week.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.4 and Appendix 3 (Section 10.3) for further details.

For more information on overdose, also consult the current version of the semaglutide s.c. investigator's brochure (IB)[43] and any updates hereof.

6.8 Concomitant therapy

6.8.1 Recording of concomitant therapy including therapies administered as part of standard of care

Concomitant therapy to be recorded in this study is concomitant medication. Any medication or vaccine (including over-the-counter or prescription medicines and COVID-19 vaccinations) that the participant is receiving at the time of randomisation or receives during the study must be recorded as concomitant medication along with:

- Trade name or generic name.
- Primary indication.
- Dose and unit, frequency, route of administration.
- Dates of administration including start and stop dates or continuation.
- Related AE number when applicable.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.4.

6.8.2 Restrictions to concomitant therapy

The following medications are prohibited during the study, in alignment with exclusion criteria #34 to #38:

- GLP-1 RAs.
- Approved or non-approved investigational medicinal product.
    - Anticholinergic medications of moderate or greater potency[a] used regularly (> 2 doses/week).
      Exceptions: Daily use of anticholinergic medications for incontinence (darifenacin, solifenacin, fesoterodine, trospium), nasal spray for rhinorrhoea (ipratropium) or inhalants for pulmonary disorders (tiotropium).
    - Benzodiazepines and sedatives used regularly (> 2 doses/week).
      Exceptions: Daily use of the following medications for sleep:
        - zaleplon ≤ 5 mg, zopiclone ≤7.5 mg, eszopiclone ≤ 3 mg, zolpidem ≤ 5 mg
        - trazodone, suvorexant, or mirtazapine.
- Any vaccine product (including booster) before visit 5.
- Use of any systemic immunomodulating drugs (small molecules and/or biologics) such as corticosteroids for systemic use, immunostimulants and immunosuppressants before visit 5.
- Use of anti-neoplastic (cancer) drugs before visit 5.

[a] The anticholinergic potency can be assessed as described in Salahudeen et al. 2015.[45]

If the investigator evaluates that continued use of a prohibited concomitant medication is required on a long-term basis the participant should permanently discontinue study intervention. If anti-parkinsonian medications are indicated, Novo Nordisk should also be contacted.

For administration of an approved Alzheimer's disease treatment (such as acetylcholinesterase inhibitors or memantine), the dose should not be changed during the study unless medically necessary. Disease-modifying treatments for Alzheimer’s disease such as anti-amyloid beta (Aβ)

drugs (e.g., lecanemab or aducanumab) is NOT allowed during *study intervention period 1* (i.e., during the first 12 weeks of treatment until visit 5). An approved Alzheimer's disease treatment can be initiated by investigators after visit 5 if deemed medically necessary. Initiation of these medications will be considered as rescue therapy.

Novo Nordisk should be contacted if there are any questions regarding concomitant or prior medication.

7 Discontinuation of study intervention and participant discontinuation/withdrawal

Study participants will be followed for the complete duration of the study irrespective of their adherence to allocated study intervention or adherence to the protocol in general. Efforts must be made to keep the participants on study intervention and to have participants attend and complete all scheduled visit procedures. Study participants must be educated about the continued scientific importance of their data, even if they discontinue study intervention.

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 1 (Section 10.1.11).

7.1 Discontinuation of study intervention

Study intervention (i.e., randomised treatment) may be discontinued at any time during the study at the discretion of the participant or at the discretion of the investigator for safety, behavioural, or compliance reasons.

Temporary discontinuation of study intervention is allowed at the discretion of the investigator. The primary reason for discontinuation of study intervention must be recorded in the eCRF. Date of last dose of study intervention should be recorded in the eCRF. Treatment discontinuation must be registered in RTSM when a participant is on treatment pause and treatment resume must be registered in RTSM when a patient resumes study intervention.

Study intervention should be resumed if the circumstances later allow. Similarly, participants who discontinue study intervention on their own initiative should be encouraged to resume the treatment.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for visit 5 and the end of treatment visit (visit 11). In case of permanent discontinuation of study intervention, the primary reason for discontinuation of study intervention must be specified in eCRF, and final drug accountability must be performed. Discontinuation of treatment must be registered in the RTSM.

Temporary or permanent discontinuation of study intervention will not lead to withdrawal from the study. Efforts must be made to have the participants who discontinue study intervention attend the planned visit schedule. As a minimum, participants who discontinue study intervention should come to visit 5 and the end of treatment visit (visit 11), where key assessments are to be made and as a minimum the primary endpoint and all secondary endpoints, as well as important safety data, should be assessed. Only participants who withdraw consent will be considered as withdrawn from the study. Details regarding participant withdrawal from the study are provided in Section 7.2 below.

7.1.1 Study intervention discontinuation criteria

Administration of study intervention (i.e., randomised treatment) may be discontinued temporarily or permanent during the study due to safety considerations.

Study participants meeting discontinuation criteria #1 to #3 are not allowed to resume study intervention if fulfilling the criteria.

Study participants meeting discontinuation criteria #4 to #10 should temporarily discontinue study intervention and study intervention can be resumed, if the criteria are no longer met. Confirmation of laboratory values and repeated testing may be performed at the local or central laboratory at the discretion of the investigator. Local test results must be documented in the participant's medical record.

The study intervention must be discontinued, if any of the following applies for the participant:
Conditions leading to permanent discontinuation of study intervention
1. Diagnosis of active hepatitis B or hepatitis C before visit 5.
2. Diagnosis of HIV before visit 5.
3. Suspected severe systemic hypersensitivity to the product

Conditions leading to temporary or permanent discontinuation of study intervention
4. Pregnancy.
5. Intention of becoming pregnant.
6. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study.
7. If acute pancreatitis is suspected, the study intervention should be discontinued. If acute pancreatitis is confirmed, the study intervention should not be restarted.
8. Administration of any of the disallowed medications (Section 6.8.2).
9. If the participant's study partner withdraws consent from the study and a replacement with another study partner fulfilling inclusion criteria #9 and #10 is not possible.
10. Other safety concerns, at the discretion of the investigator.

7.2 Participant discontinuation/withdrawal from the study

A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioural, or compliance reasons.

A participant may withdraw consent at any time at his/her own request.

If a participant withdraws consent or is withdrawn by the investigator prior to randomisation, he/she will not be asked to have any follow-up assessments performed. The following data must be collected: Demography, available eligibility criteria, date of informed consent, date of screening and the date when participant's participation ended. The end of study form must be completed.

If a participant withdraws consent or is withdrawn by the investigator after randomisation, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to the end of treatment visit (visit 11). See the flowchart for data to be collected. The end of study form must be completed.

The withdrawal date is considered to be the participant's last visit, assessment or contact in the study, whichever is the latest.

Final study intervention accountability must be performed even if the participant is not able to come to the site. Discontinuation of treatment must be registered in the RTSM.

If the participant withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent for the purpose of the study or scientific research.

This will also apply in any country(ies) relying on explicit informed consent as legal basis for processing personal data. If a participant wants to exercise any of his/her rights, he/she must follow the description in the 'Agreement to take part' form (See Section 10.1.3).

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested; the investigator must document this in the medical record and notify the sponsor as soon as possible.

Although a participant is not obliged to give his/her reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the CRF.

7.2.1 Replacement of participants

If a participant discontinues study intervention, withdraws consent or is withdrawn by the investigator, he/she will not be replaced.

7.3 Lost to follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a participant fails to return to the site for a required visit:

- The site must attempt to contact the participant and the participant's study partner and reschedule the missed visit as soon as possible and counsel the participant and the participant's study partner on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant and the participant's study partner (where possible, at least three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's source document.
- Should the participant and the participant's study partner continue to be unreachable, the participant will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 Study assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the flowchart, Section 1.2.

The following general assessments and procedures must be followed in the study:

Activities related to study enrolment

- Informed consent from both the participant and study partner must be obtained before any study-related activity, see Appendix 1 (Section 10.1.3). Consent for collection of samples for *APOE* genotyping is part of the participant informed consent form. Consent for optional collection of samples for future research (blood and CSF samples; see Section 8.10) will be obtained using a separate form.
- Prior to randomisation of the participant at visit 2, all screening evaluations must be completed and reviewed to confirm that potential participants meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, participants will be provided with a card stating that they are participating in a study and giving contact details of relevant site staff that can be contacted in case of emergency.
- The investigator should inform the participant's primary physician about the participant's participation in the study if the participant has a primary physician and if the participant agrees to the primary physician being informed.
- Each participant should be asked to provide contact information for persons (preferably at least 3), e.g., study partner, relatives, primary care provider or other, whom investigator can contact in case of issues when trying to contact the participant during the study. The sites are encouraged to maintain these details as current as possible throughout the course of the study.

Activities related to scheduled visits

- Adherence to the study design requirements, including those specified in the flowchart (Section 1.2), is essential and required for study conduct.
- The investigators must ensure they keep regular contact with each participant throughout the entire study, and at all times have updated contact information.
- It is the responsibility of the investigator to schedule visits including imaging and laboratory assessments as per protocol (see flowchart, Section 1.2) and ensure they take place. For study intervention compliance see Section 6.4.
- In cases of missed visits, the site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study. Even if a visit is missed and it is not possible to re-schedule, the investigator must take every effort to have all participants followed for endpoint-related outcomes.
- Participants and study partners should bring the dosing diary to the site at study visits 3 to 11.

Details on study procedures and assessments

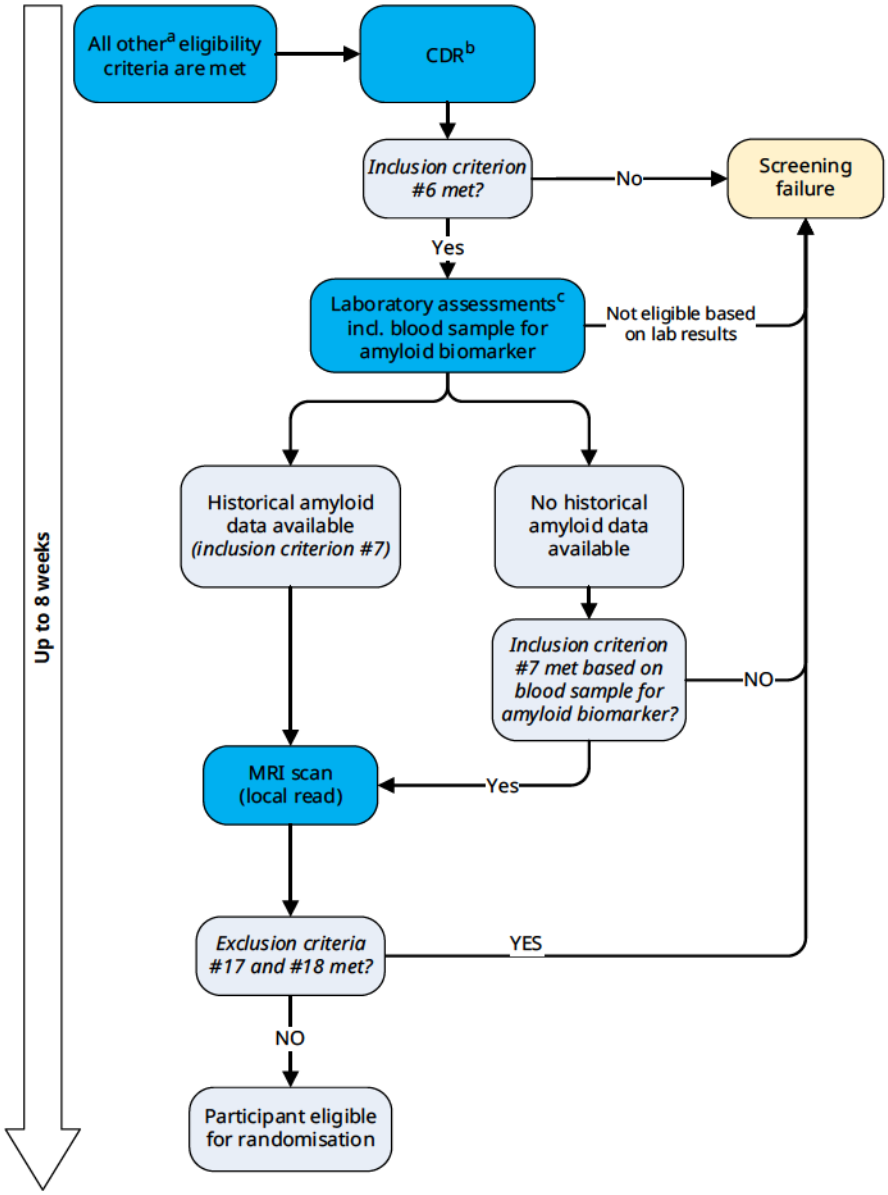
- There are no fasting visits.

- Assessments and procedures at a given study visit do not need to be performed on the same day, provided that they are completed within the visit window.
- At the randomisation visit (visit 2), all baseline procedures and assessments must be performed prior to dosing.
- Blood and CSF samples should be drawn prior to dosing at visit 2 and before drug dispensing at visit 5.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.
- Review of screening assessments, dosing diaries, ECG, laboratory reports, and results from the structural scans, etc. must be documented in the source documents or in the participant's medical record. The review must be performed by an investigator except dosing diary that can be performed by delegated site staff. If clarification of entries or discrepancies in the dosing diary is needed, the participant and/or study partner must be questioned, and a conclusion made in the participant's source documents. Care must be taken not to bias the participant. In case of detection of AEs, this should be reported as applicable
- Future biomarker testing is planned and will not be included in the clinical study report (CSR) (Sections 8.7 and 8.8).

8.1 Screening assessments

The recommended hierarchical screening procedure is illustrated in Figure 8-1. Details on rescreening participants are included in Section 5.4.1. Investigators and study sites are encouraged to keep the screening period as short as possible and within 8 weeks.

Figure 8-1 Hierarchical screening procedure



Notes: If the participant fails to meet an inclusion criterion *or* meets an exclusion criterion, stop the screening procedures and discontinue any further testing.

[a] Includes informed consent, all eligibility criteria that are not an outcome of the assessments in the figure, medical history, concomitant medication, physical examination, neurological assessment, vital signs and pregnancy test (if applicable).

[b] Monitoring of the CDR global score for completeness of the assessment forms and correct calculation using the scoring algorithm described by Morris et al.[47] will be performed by an external vendor for all participants who meet inclusion criterion #6 (Section 8.1.3). The external monitoring activities related to the CDR assessment should be completed before eligible participants can be randomised, and it must be recorded in the eCRF if the CDR score changed after monitoring.

[c] Includes biochemistry, haematology, coagulation, infection serology (HIV, hepatitis B and C), HbA_{1c}, hs-CRP, eGFR, thyroid stimulating hormone, vitamin B12 and folate. A blood sample for amyloid biomarker should be collected and assessed for all participants; however, use of historical amyloid PET, CSF $A\beta_{1-42}$ or CSF $A\beta_{1-42}/A\beta_{1-40}$ assays up to 5 years old is allowed for inclusion (inclusion criterion #7) (Section 8.1.2).

Local requirements may apply. Denmark, Sweden, and Switzerland: see country-specific requirements (Appendix 8, Section 10.8).

Abbreviations: CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.

8.1.1 Structural CNS disease and small-vessel pathology

Brain MRI scans will be performed to evaluate clinically significant structural CNS disease and small-vessel pathology at screening. The structural scans must be performed and evaluated locally in accordance with the requirements outlined in the imaging procedure manual.

Results from the structural scans will be used to determine participant eligibility according to exclusion criteria #17 and #18.

Information related to WMH using Fazekas scale and lacunar infarcts should be documented in the participant's medical records and recorded in the eCRF.

8.1.2 Amyloid positivity

Amyloid positivity will be assessed for all participants based on a blood test performed by a special laboratory, by measuring $A\beta_{42}/A\beta_{40}$ ratio and p-tau_{217}/np-tau_{217} ratio (tau phosphorylated at threonine 217/tau non-phosphorylated at threonine 217) as indicated in the flowchart (Section 1.2). For participants without historical amyloid data, the result of the blood sample for amyloid biomarker should be used to determine participant eligibility according to inclusion criterion #7.

For participants where amyloid positivity is already established, use of historical amyloid PET, CSF $A\beta_{1-42}$ or CSF $A\beta_{1-42}/A\beta_{1-40}$ assays (historical data up to 5 years old) can be used to determine participant eligibility according to inclusion criterion #7 without awaiting the result of the amyloid biomarker blood sample. Refer to Section 8.1.2.1 for further details.

Local requirements may apply. Denmark, Sweden, and Switzerland: see country-specific requirements (Appendix 8, Section 10.8).

8.1.2.1 Historical amyloid biomarker (amyloid PET scan or CSF assays)

Use of historical amyloid PET scans or CSF assays (up to 5 years old) to determine participant eligibility according to inclusion criterion #7 is allowed, at the discretion of the investigator. If amyloid positivity is not confirmed, the assessments should not be repeated with other methods and the participant should be considered a screen failure. (Section 5.4).

Historical amyloid PET scans

Use of historical amyloid PET scans can be used to determine participant eligibility according to inclusion criterion #7, at the discretion of the investigator.

For participants with historical data, the date when the historical amyloid PET scan was performed including the outcome should be recorded in the eCRF and documented in the participant's medical records.

Historical CSF $A\beta_{1-42}$ or CSF $A\beta_{1-42}/A\beta_{1-40}$ assays

Use of historical CSF $A\beta_{1-42}$ or CSF $A\beta_{1-42}/A\beta_{1-40}$ assays should have been performed by a laboratory that must be part of the Alzheimer's Association quality control programme at the time of analysis. Determination of amyloid positivity will be based on the assay cut-off values. For participants with historical data, the outcome of the historical CSF assay, type of assay, cut-off

value and actual values measured should be recorded in the eCRF and documented in the participant's medical records.

8.1.3 Clinical Dementia Rating Scale

The CDR scale is a global rating system widely used to measure disease severity and disease progression in trials and research investigating Alzheimer's disease. It is based on a semi-structured, clinician-rated interview of first an informant (study partner) and then the participant, and measures the impact of cognitive decline on daily function using the following six domains commonly affected in Alzheimer's disease:

- Cognitive domains: Memory, Orientation, and Judgement and Problem Solving.
- Functional domains: Community Affairs, Home and Hobbies, and Personal Care.

Based on clinical information obtained from the participant and informant (study partner), an individual box score ranging from 0 to 3 is determined that represents "none" to "severe" impairment for each of the six domains. The CDR global score is a composite score comprised of the 6 individual domain box scores and should be calculated using the scoring algorithm described by Morris et al.[47]. The CDR global score will be used to determine participant eligibility according to inclusion criterion #6, and results of the assessment should be documented in the participant's medical records and recorded in the eCRF (CDR global score of 0.5 or 1.0).

Monitoring of the CDR global score for completeness of the assessment forms and correct calculation using the scoring algorithm, will be performed by an external vendor, for all participants who meet inclusion criterion #6. The external monitoring activities related to the CDR assessment should be completed before eligible participants can be randomised, and it must be recorded in the eCRF if the CDR score changed after monitoring.

The CDR should always be administered to the study partner first and then to the participant. All assessments should be performed separately for the participant and study partner to limit the influence of the other person on the results.

Additional detailed information concerning administration, scoring and documentation are provided in the site instruction manual.

8.1.4 Alcohol habits

Alcohol habits (current alcohol use [units per week]) is to be recorded at baseline in the eCRF, as defined in the flowchart (Section 1.2).

Alcohol habits will be used to determine participant eligibility according to exclusion criterion #27.

8.1.5 Columbia Suicidal Severity Rating Scale

The C-SSRS is a short questionnaire to determine the risk of suicide by assessing behaviour and suicidal ideation. The C-SSRS will be administered at baseline and subsequent visits to capture changes since the last visit (Section 1.2) and results should be recorded in the participant's medical records document. Furthermore, it must be recorded in the eCRF whether the participant had any

suicidal behaviour or any suicidal ideation of type 4 or type 5 on the C-SSRS assessment. C-SSRS results will be used to determine participant eligibility according to exclusion criterion #22.

A participant must be referred to a Mental Health Professional (MHP) if:

- The participant has any suicidal behaviour *or*
- The participant has any suicidal ideation of type 4 or type 5 on any C-SSRS assessment *or*
- In the opinion of the investigator, it is necessary for the safety of the participant

If one or more of these criteria are met, the investigator should explain to the participant why the referral and psychiatric evaluation by an MHP is needed. If the participant refuses, this should be documented in the medical record and assessed if it is safe for the participant to continue study intervention. If referral is not deemed relevant, this and the reason why, must be documented in the participant's medical records. In case of detection of AEs, this should be reported as applicable according to Section 8.4.1 and Section 10.3.

8.1.6 Role of study partner

All enrolled participants must have a competent study partner who is willing to actively participate in the study and share information about the participant and themselves. The study partner must sign a separate informed consent form prior to any study-related activities as described in Section 10.1.3. The study partner is expected to have had regular interaction with the participant, in order to be able to provide meaningful input to the CDR rating scale at screening (visit 1). During the study, the study partner is responsible for all device handling and must inject the participant with study intervention once-weekly (Section 6.16.1.2). The study partner must be trained in using the pen-injector and reading its DFU (Section 6.1.2). The study partner is required to attend the screening visit (visit 1) where informant input is required for the CDR rating scale as well as visits where training in administration of study intervention and dosing instructions are provided including review of dosing diary (i.e., visits 2-11). Every effort should be made to maintain the same study partner for a given participant throughout the entire duration of the study. In the event a replacement is needed, the new study partner should be equally qualified and should understand the nature of the study and the requirements. The new study partner must also sign an informed consent form and be trained in using the pen-injector. Demographic data, including birth and relationship to the participant will be collected for each study partner.

8.2 Efficacy assessments

Efficacy of semaglutide s.c. will be assessed based on laboratory biomarkers, reflecting the study endpoints (Section 3).

Planned time points for all efficacy assessment are provided in the flowchart (Section 1.2).

8.2.1 Clinical efficacy laboratory assessments

Biomarkers of efficacy include biomarkers related to semaglutide action as well as neuroinflammatory, neurodegenerative and Alzheimer-related biomarkers. Additional efficacy laboratory assessments include blood sampling for scRNAseq, scTCRseq and proteomics as well as CSF sampling for scRNAseq, scTCRseq, proteomics and semaglutide concentration.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the flowchart (Section 1.2) and the laboratory manual. Procedures for sampling, handling, storage, labelling, and shipments of the samples must be performed in accordance with the laboratory manual.

8.2.1.1 Single-cell RNA sequencing

Single-cell RNA sequencing (scRNAseq) is a method for profiling the transcriptome of single cells in a high-throughput manner. The method allows for dissection of immune cell responses both at the level of changes in gene expression within specific cell types and changes in cell composition. Using the scRNAseq method, there is no preselection of cell types which provides an unbiased characterisation of all cell types in a given biofluid (CSF and blood).

The scRNAseq will be performed by a special laboratory. Procedures for sampling, handling, storage, labelling, and shipments of the samples must be performed in accordance with the laboratory manual.

8.2.1.2 Single-cell T cell receptor sequencing

Single-cell T cell receptor sequencing (scTCRseq) will be performed to investigate the complex TCR repertoire dynamic of T cells by profiling the unique gene expression combination at the single cell level. The TCR sequencing is performed as an integrated part of the scRNAseq which enables direct interrogation of functional response of a particular cell type.

The scTCRseq will be performed by a special laboratory. Procedures for sampling, handling, storage, labelling, and shipments of the samples must be performed in accordance with the laboratory manual.

8.2.1.3 Proteomics

Proteomics is a method for simultaneously measuring thousands of proteins in a biofluid. In this study, we will profile the CSF and plasma proteome using proteomics to explore the mechanism of action of semaglutide and to further the understanding of Alzheimer's, its complications, and other related diseases. The proteomics will be performed by a special laboratory. Procedures for sampling, handling, storage, labelling, and shipments of the samples must be performed in accordance with the laboratory manual.

8.2.2 Lumbar puncture (cerebrospinal fluid collection)

Participants will be required to undergo lumbar puncture for CSF collection as indicated in the flowchart (Section 1.2). The lumbar puncture should preferably be completed as the last study-related procedure for the given visit, but the actual order of assessments will be at the discretion of the investigator.

Information related to recent (within 3 days prior to the lumbar puncture procedure) episodes of fever, cold, hay fever attacks, allergies, head trauma with loss of consciousness (within 4 weeks prior to lumbar puncture), and use of painkillers should be recorded in the participant's medical records and eCRF.

At the investigator's discretion, the lumbar puncture may be delayed for up to 10 days, if the participant within the last week has experienced signs of infections or has complaints related to altered immune responses.

8.2.3 Dosing diaries

Dosing diaries should be completed by the study partner.

Paper dosing diaries will be used in this study and will be handed out for the first time at visit 2. The investigator or delegated site staff must train the participant and study partner in dosing diary completion, as applicable.

Information about the injection of study intervention (date, time, dose injected, and site of injection [thigh, abdomen, or upper arm]) of each dose administered should be recorded in the dosing diary. Participants and study partners will be instructed to bring the dosing diary to the site at study visit 3 to visit 11, and the investigator must ensure that the dosing diary data is reviewed and transcribed to the eCRF. Dosing details related to the first administration of study intervention performed on-site at visit 2 can be noted in the participant's medical records and recorded directly in the eCRF without completion of the dosing diary.

8.3 Safety assessments

The safety profile of semaglutide s.c. will be assessed based on monitoring of safety based on physical examination, vital signs, clinical laboratory safety assessments, concomitant illness and reporting of adverse events (AEs). Details on reporting of adverse events are provided in Section 8.4.

Planned time points for all safety assessments are provided in the flowchart (Section 1.2).

8.3.1 Concomitant illness and medical history

Medical history is a medical event that the participant experienced prior to the time point from which AEs are collected, i.e., prior to lumbar puncture at visit 2.

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other study procedures performed before lumbar puncture at visit 2.

In case of an abnormal and clinically significant finding fulfilling the definition of medical history or concomitant illness, the investigator must record the finding on the medical history/concomitant illness form in the eCRF if it is present before lumbar puncture at visit 2. Any new finding or worsening fulfilling the AE definition during the study after lumbar puncture at visit 2 must be reported (Section 8.4 and Appendix 3, Section 10.3).

All relevant concomitant illness/medical history must be recorded in the Medical History/Concomitant Illness forms with special attention to:

- History of psychiatric disorder.
- History of cardiovascular disease.
- History of any infection in past 12 months

- History of allergies

8.3.2 Physical examinations and neurological assessments

Physical examinations and neurological assessments should be performed by the investigator as indicated in the flowchart (Section 1.2).

A physical examination should be performed according to local procedures and will, as a minimum, include assessments of:

- General appearance.
- Skin.
- Thyroid gland.
- Cardiovascular system.
- Respiratory system.
- Gastrointestinal system including mouth and abdomen.
- Extremities.
- Neurological system.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any abnormal clinically relevant findings in the physical examination prior to lumbar puncture performed at visit 2 should be recorded on the Medical History/Concomitant Illness form in the eCRF in accordance with Section 8.3.1. Findings after lumbar puncture at visit 2 should be reported as AEs according to Section 8.4.

8.3.3 Body measurements

Body measurements (e.g., height and weight) will also be measured and recorded as specified in the flowchart (Section 1.2). Height should be assessed without shoes in centimetres (cm) or inches (in). Body weight should be measured in kilograms (kg) or pounds (lb), with an empty bladder, without shoes and only wearing light clothing. The exact measured values should be recorded without rounding in the eCRF using one decimal, and the same equipment should be used throughout the study.

8.3.4 Vital signs

Skin temperature, pulse rate, as well as systolic and diastolic blood pressure will be assessed in accordance with the flowchart (1.2).

Skin temperature should only be measured in connection with lumbar puncture at visit 2 and visit 5. The exact measured values should be recorded without rounding in the eCRF using one decimal.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., no use of television, cell phones). Blood pressure and pulse rate measurements will be assessed in a sitting position with a completely automated device. Manual techniques should be used only if an automated device is not available.

Blood pressure will consist of 3 systolic and diastolic blood pressure measurements with intervals of at least 1-2 minutes. An additional fourth blood pressure measurement must be performed if the first two readings on systolic or diastolic blood pressure differ by >10 mmHg. No more than four measurements should be performed.

- The mean systolic and diastolic blood pressure values are calculated based on the last 2 measurements.
- The last 2 systolic and last 2 diastolic blood pressure measurements should be recorded in the eCRF. The eCRF will calculate the mean of the last 2 measurements.

Pulse rate will be measured in connection to the blood pressure measurements.

- The mean pulse rate value is calculated based on the last 2 pulse rate measurements.
- The pulse rate for the last 2 measurements should be recorded in the eCRF. The eCRF will calculate the mean of the last 2 measurements.

8.3.5 Electrocardiograms

A 12-lead ECG will be obtained as outlined in the flowchart using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QT_c intervals.

The ECG must be interpreted (categorised as normal or abnormal, and, if abnormal, furthermore indicate whether the finding was clinically relevant), signed and dated by the investigator and filed on the participant's medical record (Appendix 1, Section 10.1.9). The ECG measures and corresponding outcomes should be recorded in the eCRF.

Any abnormal clinically relevant findings revealing baseline conditions before lumbar puncture performed at visit 2 are to be reported as concomitant illness/medical history in the eCRF (Section 8.3.1). Any clinically relevant worsening of a pre-existing condition as well as any new clinically relevant signs, symptoms or disease found as a result of the ECGs conducted after lumbar puncture at visit 2 are to be reported as AEs (Section 8.4 and Appendix 3, Section 10.3).

Additional ECG recordings can be performed at the investigator's discretion, in which case the reason is to be documented, and an AE reported if applicable.

8.3.6 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the flowchart (Section 1.2) and the laboratory manual. This includes laboratory assessments of haematology, coagulation, biochemistry, serology, pregnancy, and testing in case of systemic hypersensitivity.

eGFR will be calculated by the central laboratory based on the creatinine value using the CKD-EPI equation.[15] For the central laboratory calculation of the eGFR, information on year of birth will be collected on the laboratory requisition form (Appendix 2, Section 10.2, Table 10-2. For calculation of eGFR, 01-July of the year of birth will be used.

The investigator must review all laboratory results. Any abnormal clinically relevant findings revealing baseline conditions are to be reported as concomitant illness/medical history (Section 8.3.1). Study participants with abnormal laboratory values of specific concern, may fulfil

exclusion criteria based on laboratory values (criteria #10 to #16 and #23), and should not be enrolled in the study.

Any clinically relevant worsening of a pre-existing condition as well as any new clinically relevant signs, symptoms or disease found as a result of the laboratory safety assessments conducted after randomisation are to be reported as AEs (Section 8.4). Study participants with abnormal laboratory values of specific concern, may fulfil discontinuation criteria (criteria #1 to #2, and #4) and study intervention should be discontinued temporary or permanent as specified in Section 7.1.1.

8.3.7 Pregnancy testing

A pregnancy test must be performed in women of childbearing potential (WOCBP) at each visit, i.e., at screening, at baseline, during the treatment period and at the follow-up visit (see flowchart in Section 1.2).

- WOCBP should only be included after a negative, highly sensitive urine pregnancy test (refer to Appendix 2, Section 10.2).
- Home urine pregnancy testing may be performed between visits during the study, if additional urine pregnancy testing is required locally.
- Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.
- A pregnancy test should be performed at the end of relevant systemic exposure (at follow-up visit or at next site visit in case of premature discontinuation of study intervention).
- Additional pregnancy testing should be performed during the treatment period, if required locally; see country-specific requirements (Appendix 8, Section 10.8).

Local urine testing using a highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test is standard (Appendix 2, Section 10.2 and Table 10-2). Highly sensitive serum testing (sensitivity of 5-25 mIU/mL) is mandatory if required by local regulations or ethics committees, or to resolve an indeterminate test or to confirm a positive urine test.

8.4 Adverse events and other safety reporting

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE. The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3), along with a description of AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. The relevant events are listed below in Table 8-1.

Table 8-1 AEs requiring additional data collection

Event type	AE requiring additional data collection
Medication error	X
Misuse and abuse	X
Acute gallbladder disease [a]	X
Acute pancreatitis [a]	X
Injection site reaction	X
Neoplasms (benign and malignant)	X

a. Additional data for events of acute pancreatitis are collected on the CRF form "pancreatitis" and additional data for events of acute gallbladder disease (cholelithiasis) are collected on the CRF form "gallbladder disease"

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 3 (Section 10.3).

8.4.1 Time period and frequency for collecting AE information

All AEs and SAEs must be collected from the lumbar puncture performed at visit 2 and until the end of study visit (visit 12) in accordance with the flowchart (Section 1.2) or whenever, within the above time period, the site becomes aware of an AE or SAE.

Conditions present prior to the timepoint from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those conditions identified during screening, will be recorded as medical history/concomitant illness (Section 8.3.1).

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk or designee without undue delay but not later than within 24 hours of obtaining knowledge of the events. Similarly, the investigator must submit any updated SAE data to Novo Nordisk or designee without undue delay, but not later than within 24 hours of obtaining knowledge of the information.

Investigators are not obligated to actively seek for AEs or SAEs in former study participants. However, if the investigator learns of any SAE with a suspected causal relationship to the study intervention, or to study participation, occurring after a participant has discontinued/completed the study, the investigator must notify Novo Nordisk without undue delay.

8.4.2 Method of detecting AEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about events.

8.4.3 Follow-up of AEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or until the participant is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3 (Section 10.3).

8.4.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an investigational intervention are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSARs).

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from Novo Nordisk will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

At the end of the study, when treatment is revealed, all exempted cases that meet the criteria for expedited reporting SUSARs will be submitted to the regulatory authorities. Because multiple cases will be identified simultaneously, Novo Nordisk will not be able to fulfil the 7 days requirement for fatal or life-threatening events but will within 60 days after code break have all SUSARs submitted to the regulatory authorities.

In case a regulatory authority requires the blinded report on an expedited basis, Novo Nordisk will submit individual blinded case reports related to the IMP to the relevant regulatory authorities on an expedited basis.

8.4.5 Pregnancy

It must be recorded at screening (visit 1) in the eCRF whether female participants are of childbearing potential (see Appendix 4, Section 10.4.1 for details).

Details of pregnancies, occurring between first exposure to study intervention and until follow-up (visit 12) in female participants should be collected. For details regarding collection and reporting of pregnancy information, please refer to Appendix 4 (Section 10.4).

8.4.6 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

The following disease-related outcome is common in participants with Alzheimer's disease and can be serious/life threatening:

- Dementia

As dementia is associated with the disease under study, this disease-related outcome will not be reported according to the standard process for reporting of AEs/SAEs, even though the outcome may meet the definition of an AE/SAE.

8.4.7 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form on a continuous basis. Follow up should be made regularly during the intervention period, to make sure all technical complaints are captured.

Instructions for reporting technical complaints can be found in Appendix 6 (Section 10.6).

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.5 Pharmacokinetics

Blood samples will be used to evaluate the PK of semaglutide. Residual PK samples may be used for exploratory metabolite analysis. Potential metabolite analysis will be reported separately from the CSR. PK plasma samples will be collected at the visits outlined in the flowchart (Section 1.2). The investigator must record the exact time and date for drawing the blood samples on the laboratory requisition form.

Procedures for sampling, handling, storage, labelling, and shipments of the specimens must be performed in accordance with the laboratory manual.

PK bioanalysis of analyte will be performed at a special laboratory (Attachment I). Analyte will be assayed in plasma by a validated assay. A randomisation list will be provided to the special laboratory. The bioanalytical method will be described in a bioanalytical report, and the bioanalytical report must be provided before finalisation of the CSR.

Genetic analyses will not be performed on the PK samples. The confidentiality of study participants will be maintained.

The residual PK samples will be disposed no later than final CSR.

Results of the PK analyses will not be shared with the investigator.

8.6 Pharmacodynamics

Not applicable.

8.7 Genetics

8.7.1 *APOE* genotype

A mandatory blood sample will be collected at randomisation (visit 2) to obtain DNA for *APOE* genotyping as specified in the flowchart (see also Appendix 2 [Section 10.2]). The DNA sample will only be used for the purpose of determining *APOE-ε4* status (carrier versus non-carrier). Individual test results will not be given to participants. Only central laboratory staff will have access to the samples. The samples will be coded, and the participant's identity will remain anonymous. During the conduct of the study the samples will be stored at the central laboratory and no later than at the end of study, samples will be destroyed according to local laws and regulations.

Details on processes for collection, shipment and destruction of these samples can be found in the laboratory manual.

8.7.2 Future analysis

Blood samples for DNA (genetic) analysis will be collected from participants who have consented to participate in the future analysis component of the study. Participation in the future research is optional. Participants who do not wish to participate in the future research may still participate in the study.

Samples will be collected according to the flowchart (Section 1.2). In the event of sample handling failure, a replacement genetic blood sample may be requested from the participant. Refer to Appendix 5 (Section 10.5) for further details.

Genetic samples are collected for future research. Refer to Section 8.10 for further details and Appendix 7 (Section 10.7) for retention.

8.8 Biomarkers

Collection of blood and CSF samples for biomarker research is part of this study (Section 8.2.1 and Appendix 2, Section 10.2). The following samples are required and will be collected from all participants in this study: blood and CSF, in accordance with the flowchart (Section 1.2).

Collection of samples for biomarker investigation for clinical decision is part of this study. The following samples are required and will be collected from all participants in this study:

- Blood sample for amyloid biomarker to confirm amyloid positivity.
  - $A\beta_{42}/A\beta_{40}$ ratio and $p\text{-}tau_{217}$ /$np\text{-}tau_{217}$ ratio (tau phosphorylated at threonine 217/tau non-phosphorylated at threonine 217)

In addition, biomarker investigation not used for clinical decision:

- CSF sample for amyloid biomarker to confirm amyloid positivity.
  - $A\beta_{1\text{-}42}$ and $A\beta_{1\text{-}42}/A\beta_{1\text{-}40}$ ratio

The outcome of the analyses for the amyloid biomarker investigations will be shared with the study sites according to the local requirements.

Local requirements may apply. Denmark, Sweden, Switzerland, and United States of America: see country-specific requirements (Appendix 8, Section 10.8).

Collection of samples for exploratory biomarker investigation for research and hypothesis generation is part of this study. No clinical decisions can be made based on exploratory data. The following samples will be collected from all participants in the study:

- Blood sample biomarkers related to semaglutide action as well as neuroinflammatory, neurodegenerative and Alzheimer-related biomarkers.
- CSF sample biomarkers related to semaglutide action as well as neuroinflammatory, neurodegenerative and Alzheimer-related biomarkers.
- Profiling of the CSF and plasma proteome will be performed using proteomics to explore the mechanism of action of semaglutide and to further the understanding of Alzheimer's, its complications, and other related diseases.

For the exploratory biomarkers, results are unlikely to have clinical utility on an individual level. Furthermore, the analyses will be done on pseudonymised data. Therefore, any outcome of the analyses will not be reported directly to participants or study sites. The results may be reported in publications, at scientific conferences or to authorities.

All samples must be collected and processed in accordance with the laboratory manual.

Analysis of biomarker analytes will be performed at Novo Nordisk, or a laboratory designated by Novo Nordisk.

The investigator may not be able to review the results of biomarker assessments due to risk of unblinding or because the samples are analysed after last participant's last visit.

Genetic analyses will not be performed on these blood and CSF samples. Participant confidentiality will be maintained.

Biomarker samples will be destroyed no later than at finalisation of the CSR.

Biosamples are also collected for future biomarker analysis. Refer to Section 8.10 for further details and Appendix 7 (Section 10.7) for retention.

8.9 Immunogenicity assessments

Anti-drug antibody (ADA) serum samples will be collected as specified in the flowchart (Section 1.2). All samples must be drawn prior to administration of study intervention if administration of study intervention is planned on the sampling day. ADA samples will be collected, but analysis for anti-drug antibodies will only be analysed if deemed necessary for clarification of unexpected drug exposure or other safety issues that may be related to antibody formation. If anti-semaglutide binding antibodies are measured, data as well as assay method description will be reported outside the CSR for this study.

Assessment of antibodies against drug in serum will be performed by Novo Nordisk or by a special laboratory appointed by Novo Nordisk.

The investigator may not be able to review the results of immunogenicity assessment due to the risk of unblinding.

Anti-drug antibody samples may be retained for further characterisation of immune responses towards the trial product, if required by health authorities or for safety reasons. These samples may also be used for assay maintenance or further development of anti-drug antibody assays, or for exploratory investigation of antibodies.

The antibody samples will be stored at Novo Nordisk, or a special laboratory designated by Novo Nordisk after end of study until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of study after which they will be destroyed. The samples might be transferred to other countries, if not prohibited by local regulations. Only relevant Novo Nordisk staff, consultants, auditors, research organisations or laboratories working for or collaborating with Novo Nordisk as well as storage facility employees will be able to access the stored samples and associated data.

8.10 Human biosamples for future research

Collection of biosamples for future analysis is a component of this study. The samples will be stored in a biobank and allow for future analyses when new knowledge or improved testing technologies may have become available during or after the study. Participation is optional, and participants must sign a separate informed consent to indicate their participation in the biobank component(s) of the study. Participants who do not wish to participate in the biobank component(s) may still participate in the study. Biosamples will be collected and stored for future research according to Appendix 7 (Section 10.7).

Future analyses may include investigation of inflammatory and other relevant markers expression level with the purpose of understanding and predicting the response to semaglutide as well as to understand Alzheimer's disease or related conditions.

Future analyses of circulating biomarkers will measure proteins, hormones, metabolites or other non-genetic blood entity with the purpose of understanding and predicting the response to semaglutide as well as to understand Alzheimer's disease or related conditions.

The samples may be analysed as part of a multi-study assessment. Results will not be reported to the investigator for assessments of AEs nor will they be part of the CSR. The primary objective of the analysis is to investigate on a population level and results are very unlikely to have clinical utility on an individual level. Furthermore, the analyses will be done on pseudonymised data. Therefore, any outcome of the analyses will not be reported directly to participants or sites. The result may be reported in publications, at scientific conferences or to authorities.

The human biosamples for future research will be stored for up to 15 years after end of study at a central laboratory or appropriate storage facility (see Appendix 7 (Section 10.7)).

8.11 Demography and other baseline assessments

Participant

Demographic data for the participant are to be recorded in the eCRF at screening (visit 1) and consists of:

- Birth (according to local regulation).
- Sex.
- Race (according to local regulation).
- Ethnicity (according to local regulation).
- Years of education.

Race and ethnicity must be self-reported by the participant.

It must be recorded at screening (visit 1) whether female participants are of childbearing potential (see details in Appendix 4, Section 10.4). A female participant is considered fertile following menarche and until becoming postmenopausal unless permanent sterile. If fertility is unclear (e.g., amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose study intervention, additional evaluation should be considered.

Study partner

Demography data for the study partner are to be recorded in the eCRF at screening (visit1) and consists of:

- Birth (according to local regulation).
- Relationship to the participant (according to local regulation).

Local requirements may apply. Switzerland: see country-specific requirements (Appendix 8, Section 10.8).

8.12 Tobacco and nicotine products use

Tobacco and nicotine products use is to be recorded in the eCRF at baseline, as defined in the flowchart (Section 1.2). Tobacco use/smoking is defined as smoking at least one cigarette or equivalent daily.

9 Statistical considerations

Analysis and reporting will be done and reported separately after *study intervention period 1* and *study intervention period 2*.

The statistical analysis plan (SAP) will be finalised prior to unblinding, and it will include a more technical and detailed description of the statistical analyses described in this section.

9.1 Statistical hypotheses

The primary aim is to investigate if semaglutide s.c. changes inflammation-related gene expression in immune cells from baseline to 12 weeks in CSF and blood compared to placebo in participants with Alzheimer's disease. The following two statistical tests of the co-primary endpoints will be performed jointly on a one-sided 2.5% significance level.

- Greater number of differentially expressed genes since baseline in immune cells in CSF after 12 weeks of treatment with semaglutide s.c. versus placebo.
- Greater number of differentially expressed genes since baseline in immune cells in blood after 12 weeks of treatment with semaglutide s.c. versus placebo.

9.1.1 Multiplicity adjustment

For the co-primary endpoints, the family-wise error rate will be controlled in the strong sense at $\alpha = 0.025$ by requiring the test for each associated hypothesis to be significant on a one-sided 2.5% level. For secondary and exploratory analyses testing will be done at a nominal significance level of 0.05 with no adjustment for multiple testing across analyses. When appropriate, adjustment for multiple testing will be done separately for individual analyses of gene expression data and proteomics data where methods for controlling false discovery rates will be applied.

9.2 Analysis sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set (FAS)	All randomised participants.
Safety analysis set (SAS)	All participants who are exposed to investigational intervention.

The full analysis set will be used to analyse the endpoints and assessments not related to safety and the safety analysis set will be used to analyse the endpoints and assessments related to safety.

For analyses not related to safety, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received.

9.3 Statistical analyses

9.3.1 General considerations

For confirmatory endpoints controlled for multiplicity, one-sided p-values will be used for the associated tests. For reporting of results, the estimated treatment effects will be accompanied by two-sided 95% confidence intervals and p-values.

The latest available measurement, at or prior to the randomisation visit, will be used as the baseline measurement. If no measurement(s) has been obtained, at or prior to randomisation, the baseline value will be left missing.

9.3.2 Primary endpoints analysis

9.3.2.1 Definition of endpoints

The co-primary endpoints are the number of differentially expressed genes in immune cells in respectively CSF and blood at 12 weeks compared to baseline.

The endpoints will be derived using identical methodology based on single-cell transcriptomics data in CSF and blood, respectively. The methods for determining whether a cell is an immune cell and whether expression of a given gene expression changed within the participant from baseline to week 12 will be prespecified in the SAP prior to DBL.

9.3.2.2 Main analytical approach

The analyses addressing the hypotheses for the co-primary endpoints will be based on the full analysis set (FAS). For CSF and blood respectively, the number of differentially expressed genes in immune cells at 12 weeks compared to baseline will be analysed using Welch's unequal variances t-test with treatment as grouping factor.

9.3.2.3 Sensitivity analyses

No sensitivity analyses are planned.

9.3.2.4 Supplementary analyses

No Supplementary analyses are planned.

9.3.3 Secondary endpoints analysis

For details on analyses of supportive secondary endpoints, please refer to the SAP.

9.3.4 Exploratory endpoints analysis

Exploratory endpoints and associated analyses are specified in the SAP.

9.3.5 Other safety analyses

All safety analyses will be made on the SAS. For details on analyses of safety endpoints, please refer to the SAP.

9.3.6 Other analyses

Other variables and analyses

For additional pre-specified variables and analyses, please refer to the SAP.

Pharmacokinetic and/or pharmacodynamic modelling

Population PK analysis based on the semaglutide concentration data from the study will be performed.

The objective of the population PK analysis is to evaluate exposure levels of semaglutide s.c. in Alzheimer's disease patients. More technical and detailed elaboration of the population PK analysis will be given in a modelling analysis plan (MAP), which will be prepared before the second DBL.

The population PK analysis will be reported in a separate modelling report, which will not be part of the CSR.

9.4 Interim analysis

No interim analysis is planned.

9.5 Sample size determination

Due to the exploratory nature of this study and the complexity of the collected data, no formal sample size calculation has been made for this study. Instead, the sample size has been informed by related studies that have been reported in the scientific literature. The sample size of 24 participants randomised 1:1 was chosen to enable 10 completing participants per arm, with a 20% drop-out rate. This sample size is twice as big as the one used in a recent study using a similar approach to study the differences between patients with Alzheimer's disease and healthy controls.[34]

9.6 Reporting of the main part of the study

A DBL will be performed at the end of *study intervention period 1* when all participants have completed visit 5 to be able to report the results in the first CSR. After completion of *study intervention period 2* there will be a second DBL followed by reporting of the results of the entire study in the second CSR.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[48] and applicable ICH Good Clinical Practice (GCP) Guideline[49].
- Applicable laws and regulations

The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

Regulatory authorities will receive the clinical trial application, protocol amendments/*modifications*, reports on SAEs, and the CSR according to national requirements.

Any amendments/*modifications* to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate safety hazard to study participants. In case of changes made to eliminate an immediate safety hazard, the actions must be reported to Novo Nordisk immediately (within 24 hours after the action was taken).

Before a site is allowed to start screening participants, written notification from Novo Nordisk must be received.

The list of investigator responsibilities below reflects global GCP requirements. Certain activities related to IRB/IEC submission can be carried out by the sponsor, in accordance with local or regional regulatory requirements.

The investigator will be responsible for:

- providing written summaries of the status of the study annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CSR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately (within 24 hours after discovery). A serious breach is a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of data generated in the clinical study. This includes persistent or systematic non-compliance with ICH GCP E6 and/or the protocol.

The sponsor will report any serious breach occurring in any participating country to the health authorities according to applicable regulations/laws.

Local requirements may apply. US: see country-specific requirements (Appendix 8, Section 10.8).

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and one year after completion of the study.

For US sites: Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and the participant's study partner and answer all questions regarding the study. This includes the use of an impartial witness where required according to local requirements.

The investigator must ensure the participant ample time to come to a decision whether or not to participate in the study.

Participants must be informed that their participation is voluntary. Participants and their study partners will be required to sign and date a statement of informed consent ('Agreement to take part' form) that meets the requirements of local regulations, ICH GCP[49] guidelines, Declaration of Helsinki,[48] privacy and data protection requirements, where applicable, and the IRB/IEC or site.

The medical record must include a statement that written informed consent was obtained before any study-related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any study-related activity.

The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.

Participants and their study partners must be re-consented to the most current version of the informed consent form(s) during their participation in the study according to sponsor instructions.

A copy of the informed consent form(s) must be provided to the participant and the participant's study partner.

Separate informed consent forms are available for various other situations, Informed consent must be obtained before activities related to these are undertaken:

- Male partner of a female participant in case of an abnormal pregnancy (Appendix 4 , Section 10.4.3.
- Biosamples for future research (blood and CSF samples):

- Genetic testing (Appendix 5, Section 10.5). The investigator must explain to each participant the objectives of the genetic testing. Participants must be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study period.
- Long-term storage of human samples and the use of samples for optional exploratory research (Appendix 7, Section 10.7). The investigator must explain to each participant the objectives of the exploratory research. Study participants must be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4 Recruitment and information to participants during the study

The site will be offered a communication package for the participant and study partner during the conduct of the study. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the participants and study partners. The written information will be translated and adjusted to local requirements and distributed to the participant and study partner at the discretion of the investigator. The participant and study partner may receive a "thank you for your participation letter" after completion of the study. Further, the participant and study partner may receive other written information during the study.

All written information to participants must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

10.1.5 Data protection

Participants will be assigned a 6-digit unique identifier, a subject ID. Any participant records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the participant are transferred to Novo Nordisk.

The participant and any biological material obtained from the participant will be identified by subject ID, visit number and study ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of participants as required by local, regional and national requirements.

The participant must be informed about his/her privacy rights, including that his/her personal study-related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Personal data may be collected from participants due to process requirements from Novo Nordisk's suppliers. This data is needed to ensure that the relevant data analysis for the study can be performed, but will not be part of the data transferred to Novo Nordisk, the assessment of the study endpoints or the clinical study report. A list of any such data values must be kept as part of the study documentation along with an explanation of why it was required.

The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access.

In case of a data security breach, appropriate actions will be taken promptly to mitigate any potential adverse effects, in accordance with the sponsors' procedures on how to respond in the event of unauthorized access, use or disclosure of sponsor information or systems.

Local requirements may apply. Denmark: see country-specific requirements (Appendix 8, Section 10.8).

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal study-independent ad hoc group may be established in order to maintain the blinding of the study personnel.

10.1.7 Dissemination of clinical study data

This is a multinational study including both EU/EEA and non-EU/EEA sites, and the end of study is defined as the global end of study. The summary of study results and layperson summary of results will be submitted within 12 months after the global end of study, as the planned statistical analyses cannot be performed until data from all sites are available.

Study information will be disclosed at clinicaltrials.gov, novonordisk-trials.com and euclinicaltrials.eu and, if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[48] the International Committee of Medical Journal Editors (ICMJE),[50] the Food and Drug Administration Amendment Act (FDAAA),[51] European Commission Requirements[1, 52, 53], and in accordance with Novo Nordisk commitment to clinical transparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

Novo Nordisk or designee is responsible for the data management of this study including quality checking of the data.

To demonstrate his/her oversight of the collected data, the investigator should sign the eCRF on a regular basis during the conduct of the study as well as at the end of the study, as described in the CRF completion guideline.

All participant data relating to the study will be recorded on eCRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The following will be provided as paper CRFs:

- Pregnancy forms
- Dosing diary

The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:

- AE forms
- Safety information forms
- Technical complaint forms to be used to report complaints on study intervention not yet allocated to a participant

Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

10.1.8.2 Monitoring

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Remote access to the source data documents by Novo Nordisk monitors and auditors can be agreed in countries where this is acceptable according to regulatory requirements and national legislation. Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the study. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[49], and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.

Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.

Quality tolerance limits (QTLs) will be predefined in the relevant monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the study database.

10.1.9 Source documents

All data entered in the CRF must be verifiable in source documentation other than the CRF.

If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the study staff making the entry.

For dosing diaries: The original of the completed dosing diaries (Section 8.2.3) must not be removed from the site, unless they form part of the CRF, and a copy is kept at the site.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Any source data generated by investigator's subcontractors must be archived and accessible by the site.
Data that is transcribed into the CRF from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

It must be possible to verify participant's medical history in source documents, such as participant's medical record.

The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.

Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical study documentation

Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the investigator for 25 years after end of study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the

retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the study. The investigator must be able to access his/her study documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other participant data will be provided in an electronic readable format to the investigator before access is revoked to the system supplied by Novo Nordisk. Site-specific CRFs and other participant data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.

Participant's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

Novo Nordisk will retain study documentation for 25 years or longer as required by local law, or as long as the information contributes to scientific purposes or product safety.

10.1.11 Study and site start and closure

First act of recruitment

The start of study is defined as the date when the clinical study will be open for recruitment of participants, i.e., the 'first act of recruitment.' The first act of recruitment is defined as the first site activation in the study.

Study or site termination

Novo Nordisk reserves the right to close the site or terminate the study at any time for any reason at the sole discretion of Novo Nordisk. If the study is suspended or terminated, the investigator must inform the participants promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

Sites will be closed upon study completion. A site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, *or* Novo Nordisk procedures *or GCP guidelines*
- inadequate recruitment of participants by the investigator
- discontinuation of further study intervention development.

10.1.12 Responsibilities

The investigator is accountable for the conduct of the study at his/her site and must ensure adequate supervision of the conduct of the study at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified study-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the study. It is the investigator's responsibility to supervise the conduct of the study and to protect the rights, safety, dignity and well-being of the participants.

A qualified physician, who is an investigator or a sub investigator for the study, must be responsible for all study-related medical decisions.

The investigator is responsible for filing essential documents (i.e., those documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced) in the investigator trial master file. The documents, including the participant identification code list must be kept in a secure locked facility so that no unauthorised persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g., by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of participants to a specific qualified physician who will be readily available to participants during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g., if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical studies in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the study or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with country-specific laws, acts and guidelines. Switzerland: For any country-specific indemnity requirements supplementing the above, please refer to country-specific requirements (Appendix 8, Section 10.8).

10.1.14 Publication policy

The information obtained during the conduct of this study is considered confidential and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the study intervention. All information supplied by Novo Nordisk in connection with this study shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this study.

The information obtained during this study may be made available to other investigators who are conducting other clinical studies with the study intervention, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this study to researchers who require access for research projects studying the same or related diseases and/or study intervention studied in this study.

Novo Nordisk may publish on its clinical studies website a redacted CSR for this study.

One investigator will be appointed by Novo Nordisk to review and sign the CSR (signatory investigator) on behalf of all participating investigators.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of studies regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this study will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CSR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire study.

At the end of the study, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases, the study results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the study concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[54]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

Where required by the journal, the investigator from each site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

10.1.14.3 Site-specific publication(s) by investigator(s)

For a multicentre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or participants, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the study.

10.1.14.4 Investigator access to data and review of results

As owner of the study database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research participants' data and will be provided with the randomisation code after results are available.

10.2 Appendix 2: Clinical laboratory tests

All study-required laboratory assessments will be performed by a central or special laboratory, except urine hCG pregnancy testing, which will be performed locally unless serum testing is required by local IRB/IEC.

The tests detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory unless otherwise specified. For requirements related to amyloid positivity (inclusion criterion #7), see Section 8.1.2. Additional tests may be performed at any time during the study as deemed necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g., to follow up on AEs, this must be done at a local laboratory.

The central laboratory will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their laboratory SOPs. These data will not be transferred to the study database. The investigator should review such values for AEs and report these according to this protocol.

The investigator must review all laboratory results for concomitant illnesses and AEs.

Description of laboratory supplies and procedures for obtaining, handling, and transportation of samples will be available in the laboratory manual provided to sites. The investigator must keep an overview, e.g., a log, of laboratory samples not handled according to the laboratory manual. In addition, the investigator must keep an overview, e.g., a log, of laboratory samples stored at site.

Laboratory samples analysed at the central and special laboratories (except immunogenicity samples stored for potential analysis of anti-semaglutide antibodies, Section 8.9) will be destroyed no later than at finalisation of the CSR or as required according to local regulations (see Appendix 8, Section 10.8). For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations (see Appendix 8, Section 10.8). Human biosamples for retention (future analysis) will be stored as described in Appendix 7 (Section 10.7).

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Pharmacokinetics	• Semaglutide plasma concentration[a]
Exploratory biomarkers (blood samples)	• Biomarkers related to semaglutide action as well as neuroinflammatory, neurodegenerative and Alzheimer-related biomarkers[a,b,c]
Blood sampling	• Blood sampling for scRNAseq[a] and scTCRseq[a] • Blood sampling for proteomics[a] • Amyloid biomarker[a]: ○ $A\beta_{42}/A\beta_{40}$ ratio, p-tau_{217} /np-tau_{217} ratio
CSF sampling	• CSF sampling for scRNAseq[a] and scTCRseq[a] • CSF sampling for proteomics[a] • Amyloid biomarker[a] ○ $A\beta_{1-42}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio • Biomarkers related to semaglutide action as well as neuroinflammatory, neurodegenerative and Alzheimer-related biomarkers[a,b,c] • Semaglutide concentration in CSF[d]
Biobank[e]	• Whole blood (for analyses of genetics and epigenetics) • Peripheral blood mononuclear cells (for characterization of T cell recognition, RNA, protein, metabolites and lipids) • Serum and plasma (for analyses of circulating biomarkers)
Biobank[e]	• CSF (for analyses of biomarkers)

Notes: [a] The test will be performed by a special laboratory; [b] Collection of samples for exploratory biomarker investigation for research and hypothesis generation is part of this study. No clinical decisions can be made based on exploratory data; [c] Biomarkers will be defined in the Statistical Analysis Plan (SAP) depending on the availability of validated biomarkers before database lock (DBL); [d] Analysis will be performed only if a validated reliable assay is available at the end of study; [e] Participants must sign and date a separate informed consent form before samples are collected (see Section 10.1.3).

Abbreviations: CSF = cerebrospinal fluid; np = non-phosphorylated; scRNAseq = single-cell RNA sequencing; scTCRseq = single-cell T cell receptor sequencing.

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• HbA_{1c}
Haematology	• Erythrocytes • Haemoglobin • Leucocytes • Differential count (eosinophils, neutrophils, basophils, monocytes and lymphocytes) • Thrombocytes • Haematocrit
Coagulation	• Prothrombin time • Activated partial thromboplastin time
Biochemistry[a]	• Alanine Aminotransferase (ALT) • Alkaline phosphatase (ALP) • Aspartate Aminotransferase (AST) • Total bilirubin • Creatinine • Potassium • Sodium
Inflammation	• High sensitivity C-reactive protein (hsCRP)
Hormones	• Thyroid stimulating hormone[b,c] (TSH)
Serology[b]	• HIV-1 and HIV-2 antibodies • Hepatitis B surface antigen (HBsAg) • Hepatitis C virus antibody
Serum[b]	• Vitamin B12 • Folate
Pregnancy testing	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[d]
Renal function	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation[15] (Chronic Kidney Disease - Epidemiology Collaboration) equation. For the central laboratory calculation of the eGFR, information year of birth will be collected on the laboratory requisition form. 01-Jul of the year of birth will be used for the calculation.
Immunogenicity	• Anti-semaglutide-antibody[e,f] (samples to be analysed only if required as specified in Section 8.9)
Other tests	• Blood sampling for *APOE* genotyping[e,g]

Notes:
[a] See Section 10.3 (Hy's Law) for details of required actions, and follow-up assessments for increased liver parameters.
[b] For screening purposes only;
[c] If TSH is abnormal, serum free T3 and T4 will also be measured;
[d] For women of childbearing potential, as needed, local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC, see Appendix 4 (Section 10.4);
[e] The test will be performed by a special laboratory.
[f] Must be collected prior to study intervention administration at visit 2;
[g] *APOE* genotyping is mandatory and included in the informed consent. See Section 8.7 for further details.
Abbreviations: eGFR = estimated glomerular filtration rate.

The results of semaglutide plasma concentrations, potential anti-semaglutide antibody results and exploratory biomarkers results will not be provided to the investigator, as these results will not be used for any clinical evaluation during the study.

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of AE

An AE is any untoward medical occurrence in a clinical study participant that is temporally associated with the use of IMP, whether or not considered related to the IMP. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events to be reported as AEs:

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected.
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected.
- Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition.
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent.

A 'lack of efficacy' or 'failure of expected pharmacological action' per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.

Events NOT to be reported as AEs:

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions. This includes those conditions identified during screening. Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.
- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is the AE.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**
  - Hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are

AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

- Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.
  Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs

- **Results in persistent or significant disability/incapacity**
  - The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
  - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
  - The following must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
    - Suspicion of transmission of infectious agents via IMP
    - Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x UNL and total bilirubin >2x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection

Adverse events requiring additional data collection
A specific event form needs to be completed for the following events.

Medication error:

- A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the participant, such as:
  - administration of wrong drug
    Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
  - wrong route of administration, such as intramuscular instead of subcutaneous
  - accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the study

participant were likely to happen as judged by the investigator, although they did not necessarily occur.

Misuse and abuse:

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g., overdose to maximise effect)
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g., overdose with the intention to cause harm)

Note: Medication error, misuse and abuse must always be reported on an AE form and the specific event form must be completed. The AE diagnosis on the AE form must reflect what occurred (e.g., accidental overdose, intentional overdose or other). If the medication error and/or misuse and abuse resulted in a clinical consequence, this must be reported on an additional AE form.

Acute gallbladder disease

Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)

Acute pancreatitis

Diagnosis requires at least two of the following criteria:[55]

- Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
- Characteristic findings of acute pancreatitis on imaging

Injection site reactions

Injection site reaction is inflammation in or damage to the tissue surrounding where a drug was injected.

Neoplasms (benign and malignant)

All neoplasms (both malignant and non-malignant) confirmed by histopathology or other substantial clinical evidence.

10.3.4 Recording and follow-up of AE and/or SAE

10.3.4.1 AE and SAE recording

The investigator will record all relevant AE/SAE information in the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event.

There may be instances when copies of source documents (e.g., medical records) for certain cases are requested by Novo Nordisk. In such cases, all participant identifiers, with the exception of the

subject ID, must be redacted on the copies of the source documents before submission to Novo Nordisk, see Section 10.1.5.

Please refer to Figure 10-1 for reporting of non-serious AEs. For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the study at the latest. For sign-off of SAE-related forms, refer to Section 10.3.5.

If an AE is considered to have a causal relationship with a concomitant medication, it is important that the suspected relationship is reported to Novo Nordisk in e.g., the alternative aetiology section on the safety information form. Novo Nordisk may need to report it to relevant regulatory authorities.

10.3.4.2 Assessment of severity

The investigator will assess severity for each event reported during the study and assign it to one of the following categories:

- **Mild**: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe**: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  Note: An AE that is assessed as severe should not be confused with an SAE. Both AEs and SAEs can be assessed as severe.

10.3.4.3 Assessment of causality

The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

Relationship between an AE/SAE and the relevant IMP should be assessed as:

- **Probable** - Good reason and sufficient documentation to assume a causal relationship.
- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to aetiology other than the IMP.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, should be considered and investigated.

The investigator should consult the current version of the semaglutide s.c. investigator's brochure[43] and any updates hereof, when making the causality assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always**

makes an assessment of causality for every event before the initial transmission of the SAE data.

The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved**: The participant has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented.
- **Recovering/resolving**: The condition is improving, and the participant is expected to recover from the event. This term may also be applicable for AEs ongoing at the time of death (where death was due to another AE).
  Note: For SAEs, this term is only applicable if the participant has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae**: The participant has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved**: The condition of the participant has not improved, and the symptoms are unchanged, or the outcome is not known.
  Note: this term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AEs in a participant before he/she died should be assessed as 'recovered/resolved', 'recovering/resolving', 'recovered/resolved with sequelae' or 'not recovered/not resolved'. An AE with a fatal outcome must be reported as an SAE.
- **Unknown**: This term is only applicable if the participant is lost to follow-up.

10.3.4.5 Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g., severe hypersensitivity reactions, Hy's law). This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognised follow-up period, the investigator should, upon request, provide Novo Nordisk with the autopsy results including histopathology.

New or updated information should be recorded in the eCRF.

The investigator will submit any updated SAE data to Novo Nordisk without undue delay, but not later than within 24 hours of receipt of the information.

10.3.5 Reporting of SAEs

SAE reporting via CRF

Relevant forms must be completed in the CRF.

For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information forms within the designated reporting timelines (see Figure 10-1):

- AE form without undue delay, but not later than within 24 hours.
- Safety information form within 5 calendar days.
- Both the AE and the safety information form must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

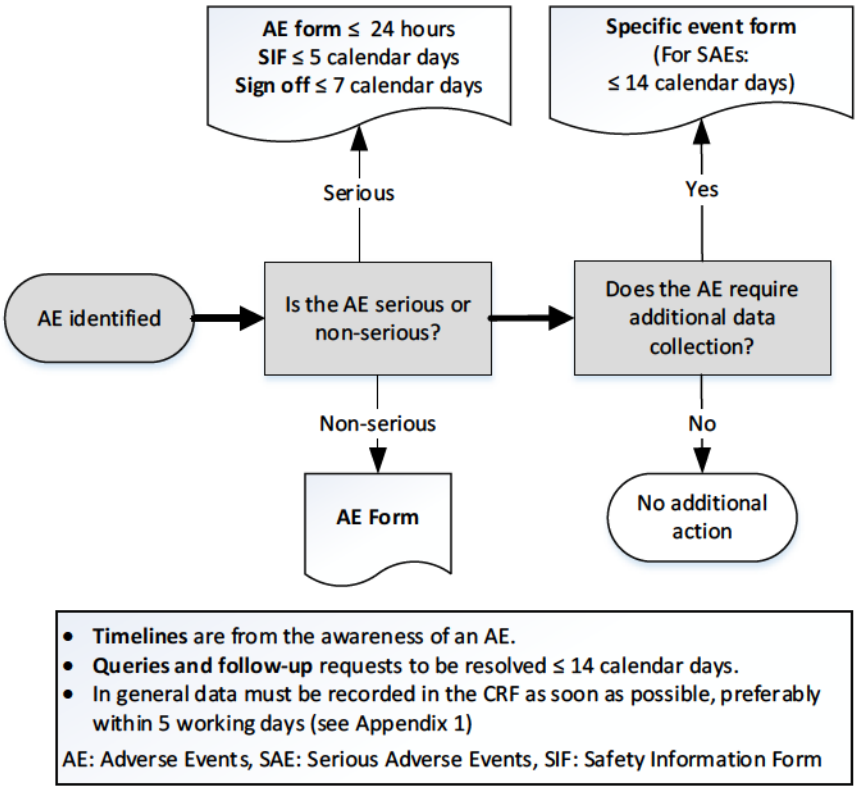
If the eCRF is unavailable for more than 24 hours, then the sites will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form. The site should enter the SAE data in the eCRF as soon as it becomes available.

The relevant CRF forms (AE and safety information forms) must be forwarded to Novo Nordisk in accordance with Appendix 1, Section 10.1.5.

After the study is completed, the study database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a new SAE from a participant or updated information on a previously reported SAE needs to be reported after CRF decommission, a paper AE and safety information form should be used to notify Novo Nordisk.

Contact details for SAE reporting can be found in the investigator trial master file and in Attachment I of the protocol.

Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines



- **Timelines** are from the awareness of an AE.
- **Queries and follow-up** requests to be resolved ≤ 14 calendar days.
- In general data must be recorded in the CRF as soon as possible, preferably within 5 working days (see Appendix 1)

AE: Adverse Events, SAE: Serious Adverse Events, SIF: Safety Information Form

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

1. Premenarcheal
2. Females with one or more of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For females with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study enrolment.
3. Postmenopausal female:
   - A postmenopausal state is defined as amenorrhoea for at least 12 months without an alternative medical cause in a female > 45 years of age. Alternative medical causes for amenorrhoea include, but are not limited to, hormonal contraception or hormonal replacement therapy.
   - Females ≥ 60 years of age can be considered postmenopausal.

Females on HRT and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the highly effective contraception methods (Table 10-3).

Note: Documentation regarding categories 1-3 can come from the site staff's review of participant's medical records, medical examination or medical history interview.

10.4.2 Contraceptive guidance

Male participants

No contraception measures are needed for male participants as the risk of teratogenicity/fetotoxicity cause by transfer of semaglutide in seminal fluid is unlikely.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly.

Highly effective contraception should be utilised for a least 35 days after last dose of IMP (corresponding to time during treatment and until the end of relevant systemic exposure).

Table 10-3 lists the highly effective methods of contraception allowed. Local regulations may apply. Denmark: see country-specific requirements (Appendix 8, Section 10.8).

Table 10-3 Highly effective contraceptive methods allowed[56]

Highly effective methods[a] (Failure rate of <1% per year when used consistently and correctly):

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
  Vasectomised partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
- Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Notes:
[a]Contraceptive use by men or women should comply with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
[b]Male condoms must be used in addition to hormonal contraception during the treatment period and for at least 35 days after the last dose of study intervention. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

The following methods are not acceptable methods of contraception: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).

10.4.3 Collection of pregnancy information

Female participants who become pregnant

Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a participant's pregnancy (see Figure 10-2).

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.

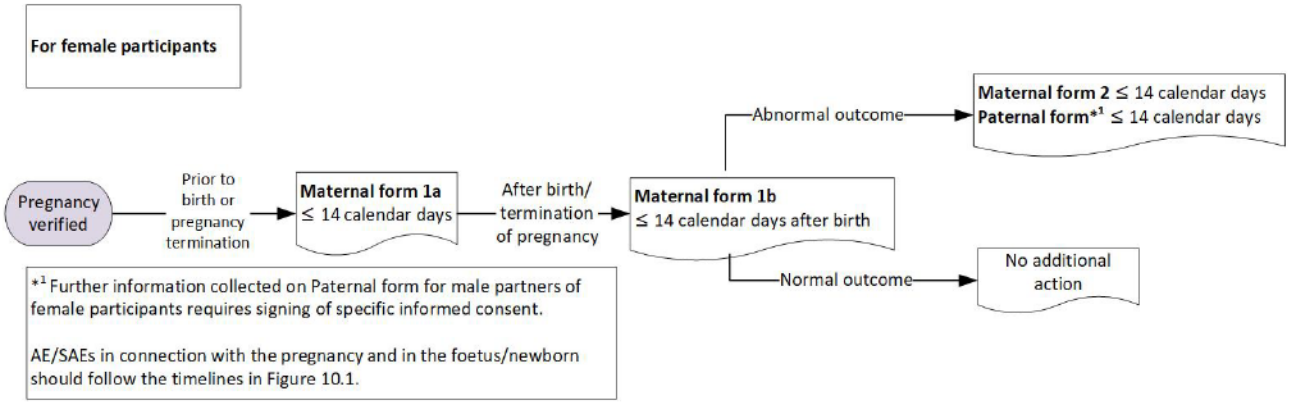
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding 'gestational', 'pregnancy-related' or a similar term when reporting the AE/SAE.

Pregnancy outcome should be documented in the participant's medical record. Abnormal pregnancy outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE. In case of abnormal pregnancy outcome, paternal information should be recorded in the appropriate form after obtaining the necessary signed paternal informed consent.

If the investigator learns of an SAE occurring as a result of a post-study pregnancy which is considered related to the IMP by the investigator, the SAE should be reported to Novo Nordisk as described in Appendix 3 (Section 10.3).

Figure 10-2 Decision tree for determining the forms to complete for collection of pregnancy information and timelines for reporting – For female participants



Any female participant who becomes pregnant while participating in the study will discontinue study intervention (Section 7.1.1). Furthermore, study intervention must be discontinued if the female participant is intent on becoming pregnant.

10.5 Appendix 5: Genetics

Use/analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism and excretion, mechanism of action of the drug, disease aetiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA analysis from consenting participants.

Blood samples for DNA analysis will be collected from participants who have consented to participant in the optional biobank component of the study (Section 8.7). Refer to Appendix 8 (Section 10.7) for further details regarding retention of human biosamples.

The specimens collected for optional genomic research will be used to identify or validate genetic markers that may increase our knowledge and understanding of semaglutide and of the biology of neuroinflammatory, neurodegenerative and other related diseases and to study the association of genetic markers with disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. The specimens may be used to also develop biomarker or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional genomic specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualised drug therapy for participants in the future. Additional analyses may be conducted if it is hypothesised that this may help further understand the clinical data.

The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to semaglutide or product treatments of this class to understand study disease or related conditions.

The results of genetic analyses will be reported in the CSR or in a separate study report.

Novo Nordisk will store the DNA samples in a secure storage space with adequate measures to protect confidentiality, as described in Appendix 8 (Section 10.7). The samples will be retained while research on study intervention of this class or indication continues, but no longer than 15 years.

10.6 Appendix 6: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.6.1 Definition of technical complaint

A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints:

- Problems with the physical or chemical appearance of study interventions (e.g., discoloration, particles or contamination).
- Problems with packaging material including labelling.
- Problems related to devices (e.g., to the injection mechanism, dose setting mechanism, push button or interface between the pen-injector and the needle).

Time period for detecting technical complaints

All technical complaints which occur from the time of receipt of the product at site until the time of the last usage of the product must be collected for products predefined on the technical complaint form.

10.6.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

For contact details for Customer Complaint Center, please refer to Attachment I.

Technical complaints on products allocated to a participant must be reported on a separate technical complaint form:

1. For products with DUN: One technical complaint form must be completed for each affected DUN.

Timelines for reporting technical complaints to Novo Nordisk

The investigator must complete the technical complaint form in the CRF within the following timelines of obtaining knowledge of the technical complaint:

- 24 hours if related to an SAE
- 5 calendar days for all other technical complaints

If the CRF is unavailable, make sure the related SAEs are reported via paper forms within 24 hours. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF. In order to report a technical complaint on a study intervention listed on the technical complaint form but not allocated to a participant, use the paper technical complaint form.

Follow-up of technical complaints

The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and all associated parts and notify the monitor within 5 calendar days of obtaining the sample at site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

10.7 Appendix 7: Retention of human biosamples for future research

10.7.1 Biosamples for future research

Study participants who do not wish to contribute with biosamples for storage may still participate in the study. Participants must sign and date a separate informed consent form before biosamples are collected to be stored for future analysis.

Human biosamples (also in some cases known as human biospecimen or human biological materials) are samples that have been taken from the human body during life or after death. This includes:

- Primary cells, tissues, organs or cell containing fluids of human origin (for example, whole blood, urine, saliva, synovial fluid).
- Cell free fluids of primary human origin (for example, serum and plasma).

Extracts or derivatives of the above, when derived by purification (for example, DNA, RNA, proteins, membranes, microsomes and other cellular substructures).

The analyses of the biosamples for future research are not intended to identify participant-specific findings, but to understand and predict response to semaglutide or Alzheimer's disease and related conditions on a population level.

In countries where allowed, and in participants providing informed consent, the study will involve collection of human biosamples to be stored in a central laboratory facility for future use as noted in Sections 8.7 and 8.8.

The material to be collected for future analysis according to the flowchart (Section 1.2):

- Whole blood
- Peripheral blood mononuclear cells
- Serum
- Plasma
- CSF

The biosamples for future research will be stored at a central laboratory, at a central storage facility or an analysing laboratory contracted by Novo Nordisk for up to 15 years after end of study. Only relevant Novo Nordisk, consultants, auditors, research organisations or laboratories working for or collaborating with Novo Nordisk as well as storage facility employees will be able to access the stored biosamples and associated data. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of study.

The participant may request the stored biosamples for future research to be destroyed by withdrawing the designated informed consent at any timepoint during and after the study. For samples that have already been analysed, the results can still be used for scientific research and will not be removed from the datafile.

The participant's identity will remain confidential, and the samples will be identified only by subject ID, visit number and study identification number. No direct identification of the participant will be stored together with the samples. Confidentiality and personal data protection will be

ensured during storage after the end of study. In the event that the collected biosamples will be used in the future, care will be taken to target analyses within the scope defined in Sections 8.7 and 8.8.

Analysis will be done on the biosamples and associated data (data relating to the test results or results from the main study). The analyses are likely to be performed after the study has come to an end, and results will therefore not be part of the CSR.

Novo Nordisk will ensure that third party collaborators live up to the regulations on data protection, see Appendix 1 (Section 10.1.5).

10.7.2 Immunogenicity samples

Remaining and residual antibody samples (see Section 8.9) already collected may be retained after end of study.

- The samples will be stored at Novo Nordisk, or a biorepository assigned by Novo Nordisk after end of study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from the end of study after which they will be destroyed.
- Only relevant Novo Nordisk staff and consultants, auditors, research organisations or laboratories working for Novo Nordisk and biorepository personnel will have access to the stored samples and associated data.
- The samples may be transferred to other countries for analysis, if not prohibited by local regulations, and will be destroyed at the latest 15 years after end of study.
- Participant's identity will remain confidential, and the samples will be identified only by subject number, visit number and study identification number. No direct identification of the participant will be stored together with the samples.
- The retained samples may be used to:
    - Evaluate safety or efficacy aspects that address concerns arising during or after the study.
    - Further characterise the antibody responses towards the drug, if required by health authorities or for safety reasons.
    - Conduct further analytical method development and validation of antibody assays.
    - Genetic analyses will not be performed on these samples.

10.8 Appendix 8: Country-specific requirements

10.8.1 Canada

No country-specific requirements apply.

10.8.2 Denmark

- Sections 5.1 (inclusion criterion #7, amyloid positivity), 8.1 (screening assessments), Figure 8-1, 8.1.2 (amyloid positivity): The criterion must be assessed using historical amyloid data (historical amyloid PET *or* historical CSF $A\beta_{1-42}$ *or* historical CSF $A\beta_{1-42}/A\beta_{1-40}$ [historical data within the last 5 years]).
- Section 5.2, exclusion criterion #4 and Appendix 4 (Section 10.4.2: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies. This means use of double barrier methods is not applicable for Denmark.
- Section 8.8 (biomarkers): Results of blood sample for amyloid biomarker ($A\beta_{42}/A\beta_{40}$ ratio and p-tau_{217}/np-tau_{217} ratio) will not be shared with the study sites or used for clinical decision.
- Appendix 1 (Section 10.1.5), Data protection: The participant must be informed about his/her privacy rights, including that his/her personal study-related data will be used by Novo Nordisk in accordance with local data protection law in the given country of data handling.

10.8.3 Sweden

- Sections 5.1 (inclusion criterion #7, amyloid positivity), 8.1 (screening assessments), Figure 8-1, 8.1.2 (amyloid positivity): The criterion must be assessed using historical amyloid data (historical amyloid PET *or* historical CSF $A\beta_{1-42}$ *or* historical CSF $A\beta_{1-42}/A\beta_{1-40}$ [historical data within the last 5 years]).
- Section 6.1: Study intervention administered: Refer to CSC for labelling requirements.
- Section 8.8 (biomarkers): Results of blood sample for amyloid biomarker ($A\beta_{42}/A\beta_{40}$ ratio and p-tau_{217}/np-tau_{217} ratio) will not be shared with the study sites or used for clinical decision.

10.8.4 Switzerland

- Sections 1.2 and 8.11: Date of birth: participant's full date of birth is not allowed to be collected and must be shortened to year of birth.
- Sections 5.1 (inclusion criterion #7, amyloid positivity), 8.1 (screening assessments), Figure 8-1, 8.1.2 (amyloid positivity): The criterion must be assessed using historical amyloid data (historical amyloid PET *or* historical CSF $A\beta_{1-42}$ *or* historical CSF $A\beta_{1-42}/A\beta_{1-40}$ [historical data within the last 5 years]).
- Section 8.8 (biomarkers): Results of blood sample for amyloid biomarker ($A\beta_{42}/A\beta_{40}$ ratio and p-tau_{217}/np-tau_{217} ratio) will not be shared with the study sites or used for clinical decision.
- Section 10.1.13: Indemnity statement: The study will be conducted in compliance with the Therapeutic Products Act (HMG/TPA) of 15 December 2000, the Human Research Act (HFG/HRA) of 30 September 2011, the Clinical Trials Ordinance (KlinV/ClinO) of 20 September 2013, the Medical Devices Ordinance (MepV/MedDO) of 1st July 2020, the

Ordinance on Clinical Trials with Medical Devices (KlinV-Mep/ClinO-MD) of 1st July 2020 and the Ordinance on In Vitro Diagnostic Medical Devices (IvDV/IvDO) of 4th May 2022.

10.8.5 United States

- Appendix 1 (Section 10.1.1), Regulatory, ethical, and study oversight considerations. All US investigators, from US sites conducted under the IND, will sign FDA Form 1572. All investigators outside of the US, including participating sites outside the US not conducted under the IND, will not sign FDA form 1572. Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the study.
- Section 8.8 (biomarkers): Results of CSF sample for amyloid biomarker (Aβ1-42 and Aβ1-42/Aβ1-40 ratio) will not be shared with the study sites.

10.9 Appendix 9: Abbreviations

Aβ	amyloid beta	IB	investigator's brochure
ADA	anti-drug-antibodies	ICH	International Council for Harmonisation
AE	adverse event	ICMJE	International Committee of Medical Journal Editors
ALT	alanine aminotransferase	IEC	independent ethics committee
AST	aspartate aminotransferase	IMP	investigational medicinal product
BMI	body mass index	INR	international normalised ratio
C_{avg}	average concentration	IRB	institutional review board
CDR	clinical dementia rating	IUD	intrauterine device
CFR	Code of Federal Regulations	IUS	intrauterine hormone-releasing system
CKD-EPI	chronic kidney disease – epidemiology collaboration	MACE	major adverse cardiovascular events
CMRglc	cerebral metabolic rates of glucose	MEN2	multiple endocrine neoplasia type 2
CNS	central nervous system	MHP	mental health professional
CRF	case report form	MRI	magnetic resonance imaging
CRP	C-reactive protein	np	non-phosphorylated
CTFG	Clinical Trial Facilitation Group	LAM	Lactational amenorrhoea
CSC	control states code	LPS	lipopolysaccharide
CSF	cerebrospinal fluid	MACE	major adverse cardiovascular events
CSR	clinical study report	MAP	modelling analysis plan
C-SSRS	Columbia Suicidal Severity Rating Scale	MCI	mild cognitive impairment
CTFG	Clinical Trial Facilitation Group	MMSE	mini-mental state examination
CVOT	cardiovascular outcome trial	NfL	neurofilament light chain
DBL	data base lock	NYHA	New York Heart Association
DFU	directions for use	OAD	oral anti-diabetic drug
DNA	deoxyribonucleic acid	PCD	primary completion date
DSM-5	Diagnostic and Statistical Manual of Mental Disorders	PD	pharmacodynamics
DUN	dispensing unit number	PET	positron emission tomography
EC	European Commission	PIN	Prostatic intraepithelial neoplasia
ECG	electrocardiogram	PK	pharmacokinetics
eCRF	electronic case report form	RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
eGFR	estimated glomerular filtration rate	RNA	ribonucleic acid
EU/EEA	European Union/European Economic Area	RTSM	Randomisation and Trial Supply Management
FAS	full analysis set	SAE	serious adverse event
FDA	U.S. Food and Drug Administration	SAP	statistical analysis plan
FDAAA	FDA Amendments Act	s.c.	subcutaneous
FU	follow-up	scRNAseq	single-cell ribonucleic acid sequencing
GCP	Good Clinical Practice	scTCRseq	single-cell T cell receptor sequencing
GI	gastrointestinal	SIF	safety information form
GLP-1	glucagon-like peptide-1	SOPs	standard operating procedures
GLP-1 RA	glucagon-like peptide-1 receptor agonist	SUSAR	suspected unexpected serious adverse reaction
GWAS	genome-wide association study	T2DM	type 2 diabetes mellitus
HbA_{1c}	glycated haemoglobin	TEAEs	treatment emergent adverse events
HBsAg	hepatitis B surface antigen	TMM	trial materials manual
hCG	human chorionic gonadotropin	TSH	thyroid stimulating hormone
HIV	human immunodeficiency virus	QTLs	quality tolerance limits
HRT	hormone replacement therapy	WMH	white matter hyperintensity
hs-CRP	high-sensitivity C-reactive protein	WOCBP	woman of childbearing potential

10.10 Appendix 10: Protocol amendment history

The Protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

Protocol version 3.0 (19 June 2024)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.[1]

Overall rationale for preparing protocol, version 3.0:

The document has been revised primarily due to an updated risk assessment, change of study countries, and clarifications regarding medical history and adverse events (AEs). Please refer to the table below for changes. In addition, editorial errors have been corrected throughout.

Deleted text is written as ~~strikethrough~~. New text is written as *italic*.

Section # and name	Description of change	Brief rationale
Title page	~~**EudraCT Number:** 2022-003384-24~~ ***EU CT Number**: 2023-506825-13*	Transitioned to EU CTR.
Section 1.2 Flowchart	Footnote j: Only AEs/SAEs ~~occurring as a result of~~ *with an onset after* the lumbar puncture performed at visit 2 should be reported. Conditions/concomitant illness present ~~at randomization~~ *before the lumbar puncture at visit 2* should be recorded as medical history/concomitant illness (Section 8.3.1);	Clarification of AE definition.
Section 1.2 Flowchart	New footnote 'o' inserted: Blood sample for immunogenicity assessment[o] *[o] All samples must be drawn prior to administration of study intervention if administration of study intervention is planned on the sampling day.* Subsequent table footnotes have been incremented.	Reminder to investigators, as this can be easily overlooked.
Section 2.3.1 Table 2-1	Intestinal obstruction added to the table as a potential risk of clinical significance: (from left to right column) *Intestinal obstruction* and: *There have been post-marketing cases of intestinal obstruction reported with semaglutide. Intestinal obstruction is a severe form of constipation with blocked passage of food, liquid and stool with additional symptoms such as stomach-ache, bloating, vomiting etc. In serious cases, intestinal obstruction can lead to bowel ischemia and perforation.* and: *Please refer to mitigations of gastrointestinal adverse events. Furthermore, participants should be informed of the characteristic symptoms of intestinal obstruction. If intestinal obstruction is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.*	Recent decision by Novo Nordisk safety committee due to post-marketing reports.

Section # and name	Description of change	Brief rationale
Section 3.1 Objectives and endpoints, and Table 3-1	Unit of exploratory endpoints related to proteomic profiles in CSF and plasma updated: ~~Normalized relative fluorescence intensities~~ *NPX, Normalized Protein eXpression.*	Vendor change, resulting in a different unit.
Section 6.8.2 Restrictions to concomitant therapy	Disease-modifying treatments for Alzheimer's disease such as anti-amyloid beta (Aβ) drugs (e.g., *lecanemab or* aducanumab) is NOT allowed during study intervention period 1 (i.e., during the first 12 weeks of treatment until visit 5).	Lecanemab added as it is now on the market.
Section 8 Study assessments and procedures	Description regarding review of dosing diary updated: The review must be performed by an investigator *except dosing diary that can be performed by delegated site staff.*	Other aspects of dosing diary activities were already delegated to site staff according to protocol, so they would be qualified to perform review.
Section 8.1.5 Columbia Suicidal Severity Rating Scale	Added text: *In case of detection of AEs, this should be reported as applicable according to Section 8.4.1 and Section 10.3.*	Reminder that responses to C-SSRS can be in scope for AE reporting.
Section 8.3.1 Concomitant illness and medical history	**Medical history** is a medical event that the participant experienced prior to the time point from which AEs are collected, i.e., prior to ~~initial dose of study intervention~~ *lumbar puncture at visit 2.* A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other study procedures performed before ~~exposure to study intervention under clinical investigation~~ *lumbar puncture at visit 2.* In case of an abnormal and clinically significant finding fulfilling the definition of medical history or concomitant illness, the investigator must record the finding on the medical history/concomitant illness form in the eCRF if it is present before *lumbar puncture at visit 2* ~~initial dose of study intervention~~. Any new finding or worsening fulfilling the AE definition during the study *after lumbar puncture at visit 2* ~~from initial dose of study intervention~~ must be reported (Section 8.4 and Appendix 3, Section 10.3).	Clarification of AE definition.
Section 8.3.2 Physical examinations and neurological assessments	*Any abnormal clinically* relevant findings in the physical examination ~~present at or~~ prior to *lumbar puncture performed at visit 2* ~~randomisation~~ should be recorded on the Medical History/Concomitant Illness form in the eCRF in accordance with Section 8.3.1. Findings *after lumbar puncture at visit 2,* ~~not present at randomisation~~, should be reported as AEs according to Section 8.4.	Clarification of AE definition.
Section 8.3.5 Electrocardiograms	Any abnormal clinically relevant findings revealing baseline conditions *before lumbar puncture performed at visit 2* are to be reported as concomitant illness/medical history in the eCRF (Section 8.3.1). Any clinically relevant worsening of a pre-existing condition as well as any new clinically relevant signs, symptoms or disease found as a result of the ECGs conducted *after*	Clarification of AE definition.

Section # and name	Description of change	Brief rationale
	lumbar puncture at visit 2 ~~randomisation~~ are to be reported as AEs (Section 8.4 and Appendix 3, Section 10.3).a	
Section 8.4 Table 8-1	Footnote a. added to table: *a. Additional data for events of acute pancreatitis are collected on the CRF form "pancreatitis" and additional data for events of acute gallbladder disease (cholelithiasis) are collected on the CRF form "gallbladder disease"*	Clarification of which CRF to use for these events.
Section 8.4.1 Time period and frequency for collecting AE information	All AEs and SAEs must be collected from the *lumbar puncture performed at visit 2* ~~randomisation visit (visit 2)~~ and until the end of study visit (visit 12) in accordance with the flowchart (Section 1.2) or whenever, within the above time period, the site becomes aware of an AE or SAE. Conditions present prior to the timepoint from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those conditions identified during screening ~~or identified during other study related procedures performed before exposure to investigational intervention~~, will be recorded as medical history/concomitant illness (Section 8.3.1).	Clarification of AE definition.
Section 8.6 Pharmacodynamics	Heading and text added: ***Pharmacodynamics*** *Not applicable.* **Note:** subsequent section 8 sub-headings are incremented which affects cross-references throughout the document, including in the Flowchart (section 1.2).	Correction to align with template requirements.
Section 8.7.2 Future analysis	Blood samples for DNA *(genetic)* analysis will be collected from participants who have consented to participate in the ~~genetic~~ *future* analysis component of the study. Participation in the ~~genetic~~ *future* research is optional. Participants who do not wish to participate in the ~~genetic~~ *future* research may still participate in the study.	Clarification that consent to future research includes the genetic analysis, they are not separate.
Section 8.8 Biomarkers	Added for CSF amyloid sample: *In addition, biomarker investigation not used for clinical decision:* • CSF sample for amyloid biomarker to confirm amyloid positivity. ○ $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ ratio The outcome of the analyses for the *amyloid* biomarker investigations ~~for clinical decision~~ will be shared with the study sites *according to the local requirements.* Sentence moved up from the bottom of this section: Local requirements may apply. Denmark, ~~Italy,~~ Sweden, ~~and~~ Switzerland*, and United States of America*: see country-specific requirements (Appendix 8, Section 10.8).	Clarification that analyses referenced includes CSF amyloid (which is not used for clinical decision) and local requirements may impact the sharing of information.
Section 8.9 Immunogenicity assessments	Sentence about anti-semaglutide antibodies added: *If anti-semaglutide binding antibodies are measured, data*	Clarification that antibody data is not part of the CSR.

Section # and name	Description of change	Brief rationale
	as well as assay method description will be reported outside the CSR for this study.	
Section 9.3.6 Other analyses	More technical and detailed elaboration of the population PK analysis will be given in a modelling analysis plan (MAP), which will be prepared before *the second* DBL.	Clarification for the PK MAP timeline.
Section 10.3.1 Definition of AE	Events NOT to be reported as AEs updated: • Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions. This includes those conditions identified during screening ~~or identified during other study procedures performed before exposure to IMP~~.	Clarification of AE definition.
Section 10.8 Country specific requirements	Requirements for Italy removed: ~~• *Sections 5.1 (inclusion criterion #7, amyloid positivity), 8.1 (screening assessments), Figure 8-1, 8.1.2 (amyloid positivity): The criterion must be assessed using historical amyloid data (historical amyloid PET or historical CSF $A\beta_{1-42}$ or historical CSF $A\beta_{1-42}/A\beta_{1-40}$ [historical data within the last 5 years]).*~~ ~~• *Section 8.3.6 and Appendix 2 (Section 10.2, clinical laboratory tests): Safety laboratory assessments will include monitoring for lipase and amylase.*~~ ~~*Section 8.8 (biomarkers): Results of blood sample for amyloid biomarker ($A\beta_{1-42}/A\beta_{1-40}$ ratio and p-tau_{217}/np-tau_{217} ratio) will not be shared with the study sites and used for clinical decision.*~~ **Note:** text references to local requirements for Italy have been removed throughout. This includes sections 5.1, 5.2, 8.1 Figure 8-1, 8.1.2, 8.8, 10.2 Table 10-2.	Italy removed as study country.
Section 10.8 Country specific requirements	Requirements for United States added: 10.8.5 United States • *Appendix 1 (Section 10.1.1), Regulatory, ethical, and study oversight considerations. All US investigators, from US sites conducted under the IND, will sign FDA Form 1572. All investigators outside of the US, including participating sites outside the US not conducted under the IND, will not sign FDA form 1572. Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the study.* • *Section 8.8 (biomarkers): Results of CSF sample for amyloid biomarker (Aβ1-42 and Aβ1-42/Aβ1-40 ratio) will not be shared with the study sites.*	USA added as study country.
Section 10.10 Protocol amendment history	Protocol amendment history added.	Section created as protocol v2.0 is superseded.
Section 11 References	Reference 1 has been corrected, which results in references 46-50 being incremented by one, and previous reference 51 is now reference 1: The European Parliament and the Council of the European Council of the European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on	Previous error in reference to the EU regulation.

Section # and name	Description of change	Brief rationale
	medicinal products for human use, and repealing Directive 2001/20/EC. ~~Annex VI – Labelling of Investigational medicinal products and auxiliary medicinal products.~~ 27 May 2014.	

Protocol version 2.0, including version 1.0: 26 April 2023, Denmark, Italy, Sweden, Switzerland

This amendment is considered to be non-substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014;[1] because it neither substantially impacts the safety or rights of the participants nor the reliability or robustness of the data generated in the study.

Overall rationale for preparing protocol, version 2.0:

Document has been revised to implement local changes requested during request for information by the Italian Medicines Agency (AIFA). In addition, country-specific requirements for Denmark, Italy, Sweden, and Switzerland have been added.

Section # and name	Description of change	Brief rationale
5.1 Inclusion criteria	Inclusion criterion #7 (amyloid positivity) updated to add country-specific requirement: *Local requirements may apply: Denmark, Italy, Sweden, Switzerland, see country-specific requirements (Appendix 8, Section 10.8).*	Inclusion for amyloid positivity (inclusion criterion #7) will be based on historical amyloid data for participants from Denmark, Italy, Sweden, and Switzerland.
8.1 Screening assessments, Figure 8-1	Footnote updated to include a reference to country-specific requirements for Denmark, Italy, Sweden, and Switzerland	To accommodate local requirements for amyloid positivity.
8.1.2 Amyloid positivity	Updated to include a reference to country-specific requirements for Denmark, Italy, Sweden, and Switzerland.	To accommodate local requirements for amyloid positivity.
8.3.6 Clinical safety laboratory assessments	Updated to include a reference to country-specific requirements for Italy.	To accommodate local requirements in Italy for monitoring of lipase and amylase.
8.8 Biomarkers	Updated to include a reference to country-specific requirements for Denmark, Italy, Sweden, and Switzerland.	Results of blood sample for amyloid biomarker ($A\beta_{1-42}/A\beta_{1-40}$ ratio and p-tau_{217} /np-tau_{217} ratio) will not be shared with the study sites or used for clinical decision in Denmark, Italy, Sweden, and Switzerland.
10.2 Appendix 2: Clinical laboratory tests, Table 10-2	Footnote a updated to include a reference to country-specific requirements for Italy.	To accommodate local requirements in Italy for monitoring of lipase and amylase.
10.8.2 Appendix 8: Country-specific requirements for Denmark	*Requirements for Denmark added:* • *Sections 5.1 (inclusion criterion #7, amyloid positivity), 8.1 (screening*	To accommodate local requirements in Denmark.

Section # and name	Description of change	Brief rationale
	assessments), Figure 8-1, 8.1.2 (amyloid positivity): The criterion must be assessed using historical amyloid data (historical amyloid PET or historical CSF $A\beta_{1-42}$ or historical CSF $A\beta_{1-42}/A\beta_{1-40}$ [historical data within the last 5 years]). • *Section 8.8 (biomarkers): Results of blood sample for amyloid biomarker ($A\beta_{1-42}/A\beta_{1-40}$ ratio and p-tau_{217}/np-tau_{217} ratio) will not be shared with the study sites and used for clinical decision.*	
10.8.2 Appendix 8: Country-specific requirements for Italy	*Requirements for Italy added:* • *Sections 5.1 (inclusion criterion #7, amyloid positivity), 8.1 (screening assessments), Figure 8-1, 8.1.2 (amyloid positivity): The criterion must be assessed using historical amyloid data (historical amyloid PET or historical CSF $A\beta_{1-42}$ or historical CSF $A\beta_{1-42}/A\beta_{1-40}$ [historical data within the last 5 years]).* • *Section 8.3.6 and Appendix 2 (Section 10.2, clinical laboratory tests): Safety laboratory assessments will include monitoring for lipase and amylase.* • *Section 8.8 (biomarkers): Results of blood sample for amyloid biomarker ($A\beta_{1-42}/A\beta_{1-40}$ ratio and p-tau_{217}/np-tau_{217} ratio) will not be shared with the study sites and used for clinical decision.*	To accommodate local requirements in Italy.
10.8.3 Appendix 8: Country-specific requirements for Sweden	Requirements for Sweden added: • *Sections 5.1 (inclusion criterion #7, amyloid positivity), 8.1 (screening assessments), Figure 8-1, 8.1.2 (amyloid positivity): The criterion must be assessed using historical amyloid data (historical amyloid PET or historical CSF $A\beta_{1-42}$ or historical CSF $A\beta_{1-42}/A\beta_{1-40}$ [historical data within the last 5 years]).* • *Section 8.8 (biomarkers): Results of blood sample for amyloid biomarker ($A\beta_{1-42}/A\beta_{1-40}$ ratio and p-tau_{217}/np-tau_{217} ratio) will not be shared with the study sites and used for clinical decision.*	To accommodate local requirements in Sweden.

Section # and name	Description of change	Brief rationale
10.8.4 Appendix 8: Country-specific requirements for Switzerland	Requirements for Switzerland added: • *Sections 5.1 (inclusion criterion #7, amyloid positivity), 8.1 (screening assessments), Figure 8-1, 8.1.2 (amyloid positivity): The criterion must be assessed using historical amyloid data (historical amyloid PET or historical CSF $A\beta_{1-42}$ or historical CSF $A\beta_{1-42}/A\beta_{1-40}$ [historical data within the last 5 years]).* • *Section 8.8 (biomarkers): Results of blood sample for amyloid biomarker ($A\beta_{1-42}/A\beta_{1-40}$ ratio and p-tau_{217}/np-tau_{217} ratio) will not be shared with the study sites and used for clinical decision.*	To accommodate local requirements in Switzerland.
11 References	References renumbered: Previous reference #1 is now #2, and one new reference is added: *1. The European Parliament and the Council of the European Council of the European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. 27 May 2014.*	For alignment.

11 References

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