Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05035082
Sponsor trial ID:	NN9924-4558
Official title of study:	REALYSE - Comparative effectiveness of once-daily oralsemaglutide versus any other oral glucose-lowering medication in a real-world adult population with type 2 diabetes on metformin monotherapy in US based health care systems - a pragmatic randomized trial.
Document date:	21 July 2025

Statistical Analysis Plan

REALYSE - Comparative effectiveness of once-daily oral semaglutide versus any other oral glucose-lowering medication in a real-world adult population with type 2 diabetes on metformin monotherapy in US based health care systems - a pragmatic randomized trial

Substance: semaglutide

Redacted statistical analysis plan
includes redaction of company confidential information.

Table of contents

Page

Table of contents 2
Table of figures 4
Table of tables 5
Version History 6
1 Introduction 7
1.1 Objectives, Endpoints, and Estimands 7
1.1.1 Primary, secondary and exploratory objectives 7
1.1.1.1 Primary objective 7
1.1.1.2 Secondary objective 7
1.1.1.3 Exploratory objectives 7
1.1.2 Primary, secondary and exploratory endpoints 7
1.1.2.1 Primary endpoint 7
1.1.2.2 Secondary endpoints 8
1.1.2.2.1 Supportive secondary endpoints 8
1.1.2.3 Exploratory endpoints 8
1.1.2.3.1 Exploratory endpoints: Exploratory phase subgroup only 8
1.1.3 Estimands 8
1.2 Study Design 10
2 Statistical Hypothesis 12
2.1 Multiplicity Adjustment 12
3 Analysis Sets 13
4 Statistical Analyses 14
4.1 General Considerations 14
4.2 Primary Endpoint Analyses 14
4.2.1 Definition of Endpoint 14
4.2.2 Main Analytical Approach 14
4.2.2.1 Statistical analysis for the primary estimand 14
4.2.2.2 Statistical analysis for the first exploratory estimand 15
4.2.3 Sensitivity Analyses 16
4.2.4 Additional Analyses 16
4.3 Secondary Endpoint Analyses 16
4.3.1 Supportive Secondary Endpoints 16
4.3.1.1 Continuous supportive secondary endpoints 16
4.3.1.2 Binary supportive secondary endpoints 17
4.3.1.3 Time to event supportive secondary endpoint 18
4.4 Exploratory Endpoints Analyses 19
4.5 Safety Analyses 19
4.5.1 Extent of Exposure 19
4.5.2 Adverse Events 19
4.6 Other Analyses 20
4.6.1 Medical history and concomitant illness 20
4.6.2 Oral semaglutide dosing 21
4.6.3 Patient-reported outcomes 21
4.6.4 Other variables 21
4.7 Interim Analysis 23
4.8 Changes to Protocol-planned Analysis 23
5 Sample size determination 24

6 Supporting Documentation 25
6.1 Appendix 1: List of abbreviations 25
6.2 Appendix 2: Definition and calculation of endpoints, assessments and derivations 27
6.2.1 eGFR 27
6.2.2 DTSQ 27
6.2.3 WPAI-GH Questionnaire 28
6.2.4 WLQ 30
6.2.5 Patient achieving individualized HbA_{1c} target per HEDIS criteria (<8.0% if age ≥65 years or with defined comorbidities or otherwise <7.0%) 30

7 References 31

Table of figures

Page

Figure 1-1 Study design....10
Figure 6-1 Adult GFR estimating equations....27

Table of tables

Page

Table 1-1 Estimands to address the primary objective....9
Table 6-1 Overview of items in DTSQs and DTSQc....28
Table 6-2 Overview of items in WPAI-GH questionnaire....29

Version History

This Statistical Analysis Plan (SAP) for study NN9924-4558 is based on the protocol *REALYSE – Comparative effectiveness of once-daily oral semaglutide versus any other oral glucose-lowering medication in a real-world adult population with type 2 diabetes on metformin monotherapy in US based health care systems - a pragmatic randomized trial* version 5.0 dated 10FEB2025.

SAP Version	Date	Change	Rationale
1.0	30AUG2021	Not Applicable	Original version
2.0	21DEC2022	The time individual patients participate in the study has been decreased from 2 years to 1 year. A few of the secondary endpoints (including key secondary endpoint) have been changed to exploratory endpoints. Sample size has been modified (in the protocol): approx. 1388 screened instead of approx. 1900 screened to achieve 1262 randomized instead of 1688 randomized. Minor clarifications to statistical analyses have been made.	To ensure study completion within business critical timelines with sufficient number of patients for securing adequate power to analyze the primary endpoint. As it is no longer a 2-year study for all patients. To reflect the updated sample size calculation. To avoid confusion regarding the different statistical analyses.
3.0	14FEB2025	CCI [redacted] All associated text are removed. Additional analyses to analyze the data collected within 52±12 weeks window from randomization. Safety Analysis Set(SAS), population set to consider for all safety outputs . Reduction of the imputation model has been detailed, if the model cannot be fit.	To align with the latest protocol v5.0. Considering the real-world nature of the study, utilizing the data collected within 12 week window from the planned visit at year 1. To be more specific in understanding the population for safety related outputs. Details on handling the possible issues if the imputation model does not converge.

1 Introduction

This SAP covers specification of the statistical analyses for data on effectiveness.

Changes to the protocol-planned analyses are described in Section 4.8.

Specifications of tables, figures and listings (TFL) and other specifications not included in this SAP will be described in the mock TFL.

1.1 Objectives, Endpoints, and Estimands

1.1.1 Primary, secondary and exploratory objectives

1.1.1.1 Primary objective

The primary objective is to evaluate the effectiveness of early-initiated oral semaglutide on change in HbA_{1c} from baseline to year 1 compared with one other oral glucose-lowering medication at the discretion of the treatment provider when used as intensification in patients with type 2 diabetes (T2D) on metformin monotherapy in the primary care setting and routine clinical practice.

1.1.1.2 Secondary objective

The secondary objective is to evaluate and generate evidence for effectiveness of treatment with oral semaglutide compared to one other oral glucose-lowering medication (from baseline to year 1) with regards to:

- Patients reaching their glycemic target
- Body weight loss
- Time to treatment intensification
- Patient reported outcomes (PROs)

CCI [redacted]

1.1.2 Primary, secondary and exploratory endpoints

1.1.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From randomization to year 1	%-points

Abbreviation: HbA_{1c} = glycosylated hemoglobin A1c.

1.1.2.2 Secondary endpoints

1.1.2.2.1 Supportive secondary endpoints

Effectiveness endpoints

Endpoint title	Time frame	Unit
Patient achieving HbA_{1c} < 7.0% (Yes /No)	Year 1	Count of patient(s)
Patient achieving HbA_{1c} ≤ 6.5% (Yes/No)	Year 1	Count of patient(s)
Patient achieving HbA_{1c} < 7.0% or at least 1.0%-point reduction in HbA_{1c} (Yes/No)	From randomization to year 1	Count of patient(s)
Patient achieving ≥5% reduction in body weight (Yes/No)	From randomization to year 1	Count of patient(s)
Patient achieving individualized HbA_{1c} target per HEDIS criteria[1,2] (<8.0% if age ≥65 years or with defined comorbidities or otherwise <7.0%) (Yes/No)	Year 1	Count of patient(s)
Patient achieving HbA_{1c} <= treatment provider defined individualized target (Yes/No)	Year 1	Count of patient(s)
Relative change in body weight (%)	From randomization to year 1	%
Change in body weight (lbs)	From randomization to year 1	lbs
Time to treatment intensification (add-on) or change (switch)	From randomization to year 1	Days
DTSQc, Relative treatment satisfaction total score	Year 1	Score on a Scale

Abbreviations: DTSQc = diabetes treatment satisfaction questionnaire, change version; HbA_{1c} = glycosylated hemoglobin A1c; HEDIS = healthcare effectiveness data and information set.

1.1.2.3 Exploratory endpoints

1.1.2.3.1 Exploratory endpoints: Exploratory phase subgroup only

CCI

[redacted]

CCI

[redacted]

1.1.3 Estimands

Three estimands, (primary, first exploratory, and second exploratory), are used to address the study objectives in terms of different aspects of the treatment effectiveness and differs in the handling of the intercurrent events. The five elements defining an estimand as outlined in ICH E9(R1)[3] are specified for the three estimands in Table 1-1 below.

The following rules will be applied for the intercurrent events mentioned in Table 1-1:

- Intensification of metformin use: a more than 20% increase in the dose of metformin after randomization as compared to the metformin dose at randomization (metformin and metformin hydrochloride will be considered as the same medications) and a dosing duration of more than 21 days.
- Use of additional glucose-lowering medication: all other oral and injectable glucose-lowering medications except for subcutaneous (s.c.) and oral semaglutide, and with a dosing duration of more than 21 days.
- Initiation of s.c. or oral semaglutide: dosing duration of more than 21 days. The date of initiation is the first dosing day.

Table 1-1 Estimands to address the primary objective

Estimand category	Estimand				
	Treatment condition	**Variable / Endpoint**	**Population of interest**	**Intercurrent events and strategy**	**Population-level summary measure**
Primary	As add on to metformin	Change in HbA_{1c} from baseline to year 1	T2D patients as defined by the protocol inclusion and exclusion criteria	Treatment policy strategy for: • Premature randomized treatment discontinuation • intensification of metformin use or use of additional glucose-lowering medication Hypothetical strategy for: • Initiation of s.c. or oral semaglutide	Mean Treatment Difference
First Exploratory				Hypothetical strategy for: • Premature randomized treatment discontinuation • Intensification of metformin use or use of additional glucose-lowering medication including s.c. or oral semaglutide	
Second Exploratory		Patients achieving an HbA_{1c} < 7%		Treatment policy strategy for: • Premature randomized treatment discontinuation Composite strategy for: • Intensification of metformin use or use of additional glucose-lowering medication including s.c. or oral semaglutide	Odds Ratio

Abbreviations: HbA_{1c} = glycosylated hemoglobin A1c; s.c. = subcutaneous; T2D = type 2 diabetes.

Primary estimand

All primary, secondary, and exploratory endpoints will employ the primary estimand (except the secondary time to event endpoint):

The primary estimand will quantify the treatment effect in the target population of patients with T2D between oral semaglutide and one other oral glucose-lowering medication, both as an add-on

to metformin, in all randomized patients regardless of premature randomized treatment discontinuation or intensification in metformin use or use of additional glucose-lowering medication.

First exploratory estimand

An exploratory estimand will be employed for the CCI [redacted], secondary endpoints (except the time to event endpoint), and primary endpoint:

The first exploratory estimand will quantify the treatment effect in the target population of patients with T2D between oral semaglutide and one other oral glucose-lowering medication, both as an add-on to metformin, in all randomized patients assuming that they adhered to randomized treatment and did not intensify metformin use or use of an additional glucose-lowering medication.

Second exploratory estimand

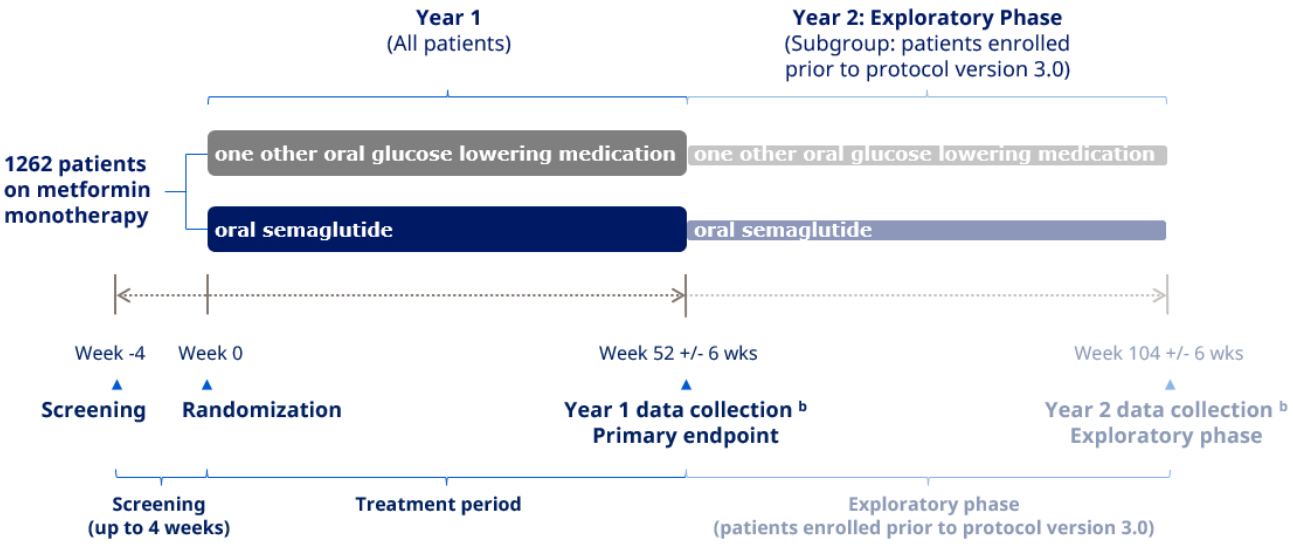
The secondary endpoint: Patients achieving HbA_{1c} <7.0% will also employ a second exploratory estimand:

In the target population of patients with T2D, what is the between group difference in the proportion of patients achieving HbA_{1c} <7.0% target after treatment with oral semaglutide compared with treatment with one other oral glucose-lowering medication both as add-on to metformin, in all randomized patients regardless of adherence to randomized treatment when intensification in metformin use or use of additional glucose-lowering medication is considered as event of not achieving HbA_{1c} <7.0% target.

1.2 Study Design

A schematic of the study design is shown in Figure 1-1.

Figure 1-1 Study design



[a] Exact number will vary based on number of patients enrolled prior to protocol version 3.0 coming into effect.
[b] Intermediate data collection from routine and additional care visits depending on local clinical practice.

For further details please refer to the protocol.

2 Statistical Hypothesis

The primary objective is to show superiority of oral semaglutide versus "one other oral glucose-lowering medication treatment group" on the primary endpoint. Superiority will be evaluated using the estimated treatment difference (ETD) (estimated change from baseline in HbA_{1c} (%) in the "oral semaglutide treatment group" minus estimated change from baseline in HbA_{1c}(%) in the "one other oral glucose-lowering medication treatment group") and the hypothesis of superiority:

$$H_0: ETD \geq 0 \text{ against } H_A: ETD < 0$$

2.1 Multiplicity Adjustment

No multiplicity adjustment will be done. The power for testing the hypothesis will be calculated. Analysis will be done for the primary estimand as described in Section 4.2.2.1.

3 Analysis Sets

For the purposes of analysis, the following analysis set is defined:

Patient Analysis Set	Description
Full analysis set (FAS)	All randomized patients. Patients will be included in the analyses according to the planned treatment.
Safety analysis set (SAS)	All randomized patients who have initiated the study drug.

The following data points sets are defined:

Data Points Sets	Description
DPS1 – period 1	All observed data points from randomization until the first date of: • End of study • Initiation of s.c. or oral semaglutide in the other glucose-lowering medication group • Initiation of s.c. semaglutide in the oral semaglutide group
DPS2 – period 2	All observed data points from first date of study product until the first date of: • End of study • Premature treatment discontinuation • Intensification of metformin use • Use of additional glucose-lowering medication • Initiation of s.c. or oral semaglutide in the other glucose-lowering medication group • Initiation of s.c. semaglutide in the oral semaglutide group
DPS3 – period 3	All observed data points from randomization until end of study.
DPS4 – period 4	All observed data points from first date of study product until permanent discontinuation of treatment.

FAS and DPS1 are used to estimate the primary estimand. FAS and DPS2 are used to estimate the first exploratory estimand. FAS and DPS3 are used to estimate the second exploratory estimand. SAS and DPS4 are used to evaluate safety related data.

Please refer to Section 1.1.3 for a list of rules applicable for the data point sets mentioned above.

4 Statistical Analyses

4.1 General Considerations

Data from all sites and health systems will be analyzed and reported together.

Results from a statistical analysis will, as a minimum, be presented by the ETD for oral semaglutide vs. one other oral glucose-lowering medication with associated two-sided 95% confidence intervals and p-values corresponding to unadjusted two-sided tests of no difference with significance level of $\alpha = 5$ %.

If no statistical analysis is specified, data will be presented using relevant summary statistics. Continuous variables will be summarized descriptively with minimum, maximum, mean, standard deviation, median, 5% and 95% percentile. Descriptive summaries will contain all measurement time points (see flowchart in the protocol).

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

4.2 Primary Endpoint Analyses

The primary endpoint will be analyzed using the primary estimand and the first exploratory estimand (see Section 1.1.3).

4.2.1 Definition of Endpoint

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in HbA_{1c}	From baseline to year 1	%-points	The baseline HbA_{1c} will be the patient's most recent HbA_{1c} within 90 days prior to randomization. If value is not available at the required year 1 visit (V3), the closest HbA_{1c} value ±10 weeks from the year 1 target visit (i.e. week 52) is accepted if available.

Abbreviations: HbA_{1c} = glycosylated hemoglobin A1c.

4.2.2 Main Analytical Approach

4.2.2.1 Statistical analysis for the primary estimand

The primary estimand will be estimated based on the FAS using data from all patients with observations at the required study visit at year 1 (V3), with the exception of data collected from patients who, in violation of the protocol, have initiated s.c. or oral semaglutide in the one other oral glucose-lowering medication treatment group or initiated s.c. semaglutide in the oral semaglutide treatment group (i.e. DPS1 as defined in Section 3). The data collected following any such initiations will be excluded for this estimand and instead imputed together with missing data. The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with

treatment as a categorical effect, and baseline HbA_{1c} as covariate. From the model, the ETD (oral semaglutide versus one other oral glucose-lowering medication) will be presented together with the corresponding two-sided 95% confidence interval and the unadjusted two-sided p-value for testing the null-hypothesis of no difference.

Prior to analysis, missing data will be imputed by multiple imputation. One thousand complete data sets will be generated to adequately account for the uncertainty due to missing data. Missing endpoint data will be imputed separately by treatment group and based on whether these patients are on or off randomized treatment at the required study visit at year 1 (V3). Data will be imputed based on the assumption that, within treatment groups, patients with missing endpoint data will behave like patients with the same randomized treatment status (on or off randomized treatment) at the required study visit at year 1 (V3) as the last registered treatment status prior to the required study visit at year 1 (V3) for the patients with missing endpoint data. For example, for patients withdrawing from the study with an "off randomized treatment" status, data will be imputed based on the assumption that the withdrawn patients will behave like patients who remain in the study but are not receiving randomized treatment at the required study visit. Technically, the imputation model will be an ANCOVA for the endpoint data. The ANCOVA will include baseline HbA_{1c}, diabetes duration, age, and sex as independent variables. If the imputation model cannot be fit, then the model will be reduced until the model can be fit. Reduction will be done in a fixed order by first removing sex, then removing age, then diabetes duration and finally removing baseline HbA_{1c}. If the model still cannot be fit, the imputation will be done regardless of the randomized treatment arm. After this model has been used to predict missing values, each of the now 1000 complete data sets will be analyzed as described above. Finally, the multiple analysis results will be combined using Rubin's rule[4].

Superiority for the primary endpoint will be considered established if the upper limit of the 95% confidence interval for the ETD is less than 0, or equivalently if the unadjusted two-sided p-value is significant on a 5% level and the ETD is in favor of oral semaglutide for the analyses of the primary estimand. The seed for imputation will be set to 45581326.

To determine on or off randomized treatment status, information from the pages "Randomized Treatment Medication" and "End of treatment" in the electronic case report form (eCRF) are to be assessed.

4.2.2.2 Statistical analysis for the first exploratory estimand

To further evaluate the primary objective of the study, the first exploratory estimand is used, and it will be estimated based on the FAS. The analysis is similar to the analysis of the primary endpoint for the primary estimand but varies with regards to the data used and the imputation of missing data.

Specifically, data will only be used from the subset of patients who are receiving randomized treatment at the required study visit at year 1 (V3) and who did not intensify metformin dose or use additional glucose-lowering medication (i.e. DPS2 as defined in Section 3). Data from patients who are off randomized treatment at this visit or who intensified metformin dose or used additional oral glucose-lowering medication will be excluded for this estimand and imputed together with missing data.

The same will apply for patients who, in violation of the protocol, have initiated s.c. or oral semaglutide in the one other oral glucose-lowering medication treatment group or initiated s.c. semaglutide in the oral semaglutide treatment group.

Collectively, missing and excluded data will be imputed separately by treatment group based on the assumption that patients who are off randomized treatment, increased the metformin dose or used additional (oral or s.c.) glucose-lowering medication behave like patients that remain in the study and continue on randomized treatment only.

The technical aspects of missing data imputation based on multiple imputation, the statistical analysis of the multiple complete data sets, and combination of the multiple results will almost be the same as that described for the primary estimand (see Section 4.2.2.1). The only difference for the first exploratory estimand is that missing data will not be imputed based on treatment status as data from patients who are off randomized treatment will be excluded for this estimand and imputed together with missing data as described above. The seed for imputation will be set to 45582437.

4.2.3 Sensitivity Analyses

One-way tipping-point multiple imputation analyses will be conducted for the primary endpoint analyses for the primary and the first exploratory estimand by adding a penalty to the imputed values and then repeating the analyses.

4.2.4 Additional Analyses

HbA_{1c} data collected within 52± 12 weeks from randomization will be analyzed using the primary estimand and the first exploratory estimand, similar to the primary endpoint analyses. Further details on the analysis and imputation method are described in 4.2.2.

4.3 Secondary Endpoint Analyses

4.3.1 Supportive Secondary Endpoints

4.3.1.1 Continuous supportive secondary endpoints

The continuous supportive secondary endpoints will employ similar estimands as described for the primary endpoint (i.e. intercurrent events will be handled like for the primary estimand and first exploratory estimand). The same approaches for imputation and statistical analyses as specified for the primary endpoint (see Section 4.2.2) will be used for these endpoints (using baseline measurements of body weight or scores of DTSQs instead of baseline HbA_{1c}).

Type	Title	Time frame	Unit	Details
Supportive secondary endpoint	Relative change in body weight	From baseline to year 1	%	Relative change (%) = (Change in body weight (lbs) / Baseline body weight) x 100
	Change in body weight	From baseline to year 1	lbs	The date and results of the most recent assessment will be recorded at every visit. Self-reported data from virtual visits is acceptable.
	DTSQc, relative treatment satisfaction total score	Year 1	Score on a scale	Scores range from -18 to 18. Score is regarded as continuous variable (further details in Appendix 2 (Section 6.2.2).

Abbreviations: DTSQc = diabetes treatment satisfaction questionnaire, change version.

4.3.1.2 Binary supportive secondary endpoints

All binary supportive secondary endpoints will employ similar estimands as described for the primary endpoint (i.e. intercurrent events will be handled like for the primary estimand and first exploratory estimand). Furthermore, the endpoint "Patient achieving HbA_{1c} < 7.0% (Yes /No)" will also employ the second exploratory estimand. The specific details regarding the statistical analyses are specified below.

Type	Title	Time frame	Unit	Details
Supportive secondary endpoint	Patient achieving HbA_{1c} < 7.0% (Yes /No)	Year 1	Count of patient(s)	
	Patient achieving HbA_{1c} ≤ 6.5% (Yes/No)	Year 1	Count of patient(s)	
	Patient achieving HbA_{1c} < 7.0% or at least 1.0%-point reduction in HbA_{1c} (Yes/No)	From baseline to year 1	Count of patient(s)	
	Patient achieving ≥5% reduction in body weight (Yes/No)	From baseline to year 1	Count of patient(s)	
	Patient achieving individualized HbA_{1c} target per HEDIS criteria (<8.0% if age ≥65 years or with defined comorbidities or otherwise <7.0%) (Yes/No)	Year 1	Count of patient(s)	Defined comorbidities based on the eCRF page "Medical History / Concomitant Illness". See details in Appendix 2 (Section 6.2.5)
	Patient achieving HbA_{1c} <= treatment provider defined individualized target (Yes/No)	Year 1	Count of patient(s)	

Abbreviations: eCRF = electronic case report form; HbA_{1c} = glycosylated hemoglobin A1c; HEDIS = healthcare effectiveness data and information set.

Statistical analyses for the primary and first exploratory estimand

The binary supportive secondary endpoints will be analyzed using a logistic regression model with a logit link function, treatment as a categorical effect, and baseline value (HbA_{1c} resp. body weight) as covariate. From the model, the estimated odds ratio (oral semaglutide versus one other oral glucose-lowering medication) will be presented together with the corresponding two-sided 95% confidence interval and the unadjusted two-sided p-value for testing the null-hypothesis of no difference.

Otherwise, the same approaches for imputation and statistical analyses as specified for the primary endpoint (see Section 4.2.2) will be used for the binary endpoints. Imputations are done on the continuous scale (HbA_{1c} resp. body weight) and subsequently dichotomized for the binary endpoint. For the odds ratio, the multiple analysis results will be combined on the logarithmic scale (using Rubin's rule as for the primary endpoint).

Statistical analysis for the second exploratory estimand

The observed data (DPS3 data set from Section 3) at the required study visit at year 1(V3) will determine the response status for patients who did not intensify metformin use and did not use additional glucose-lowering medication (including s.c. and oral semaglutide) during year 1. Patients who intensify metformin use or use additional glucose-lowering medication (including s.c. or oral semaglutide) during year 1 will be classified as non-responders. Otherwise, the technical aspects of missing data imputation based on multiple imputation, the statistical analysis of the multiple complete data sets, and combination of the multiple results will be the same as that described for the primary estimand (see Section 4.2.2.1).The seed for imputation will be set to 22071437.

4.3.1.3 Time to event supportive secondary endpoint

The following rules will be applied based on the concomitant medication data (i.e. using the "Concomitant Medication" eCRF page) to determine whether the recorded additional glucose-lowering medication (including s.c. or oral semaglutide; see below for details) is either

1. *Intensification of metformin use:*
    a. a more than 20% increase in the dose of metformin after randomization as compared to the metformin dose at randomization (metformin and metformin hydrochloride will be considered as the same medications),
    b. dosing duration of more than 21 days,

or

2. *New glucose-lowering medication:*
    a. anti-diabetic medication (4th-level ATC code) that is initiated after randomization,
    b. new compared to the anti-diabetic background medication (i.e. metformin) at randomization,
    c. dosing duration of more than 21 days.

Type	Title	Time frame	Unit	Details
Supportive secondary endpoint: time to event	Time to treatment intensification (add-on) or change (switch)	From randomization to year 1	Days	Regards additional glucose-lowering medication (including s.c. or oral semaglutide; see below for details) initiated after randomization and before the required (planned) year 1 visit (V3).

If a patient in the one other oral glucose-lowering medication group initiates s.c. or oral semaglutide, or if a patient in the oral semaglutide group initiates s.c. semaglutide, this will be categorized as *new glucose-lowering medication* (even though these events are protocol violations). Furthermore, it will be considered an event regardless of adherence to randomized treatment. The latter holds for the event of metformin intensification as well.

The analysis will be based on the FAS and DPS1 data set, and it will be carried out using a Cox proportional hazards model with treatment as categorical effect and baseline HbA_{1c} as a covariate. From this analysis, the estimated hazard ratios between oral semaglutide and one other oral glucose-lowering medication together with associated two-sided 95% confidence intervals and unadjusted two-sided p-values will be presented.

The analysis aims to address the need of additional glucose-lowering medication regardless of whether this is due to lack of effect or tolerability. Withdrawn patients or patients lost to follow-up will be considered as having an event on the day of withdrawal. Patients having no events will be censored on the day before the required (planned) year 1 visit (V3).

The time to event endpoint described in this subsection is used as a medication persistence measure in this study.

4.4 Exploratory Endpoints Analyses

4.5 Safety Analyses

The safety data will be evaluated based on the SAS using the DPS4 data set (see Section 3) unless otherwise stated.

4.5.1 Extent of Exposure

Duration of exposure will be summarized categorically by treatment group for the DPS4 data set.

In addition, time on study product and treatment pause will be summarized descriptively just like the other continuous endpoints (additionally, total time in days and years will be reported).

4.5.2 Adverse Events

Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) coding. A treatment-emergent AE is defined as an AE with onset in the period 4 duration (see Section 3).

The following assessments will be done and summarized by means of the number of patients with at least one event (N), the proportion of patients with at least one event (%), the number of events (E) and the event rate (R) per 100 patient years of exposure time for the DPS4 data set (resp. per 100 patient years of observation time for the DPS3 data set):

- Serious adverse events (SAEs)
- Adverse events (AEs) leading to discontinuation of randomized treatment
- AEs of COVID-19, irrespective of seriousness. Note: Suspected COVID-19 should be reported if the clinical presentation is suggestive of COVID-19, even in the absence of a COVID-19 test or without a positive COVID-19 test result. In the absence of clinical symptoms, a positive COVID-19 test (antigen or antibody) should be reported, if available.
- Medication errors, misuse, and abuse

Summaries will be presented as overall, by relationship to study product, by severity, by seriousness, by outcome, by treatment discontinuation status and by action taken to study product. Total exposure time (i.e. period 4) and observation time (i.e. period 3) in years will be presented in the summary as well.

In addition, treatment emergent SAEs and AEs leading to discontinuation of randomized treatment will be summarized by system organ class and preferred term (DPS4 data set).

The development over time in AEs leading to discontinuation will be presented graphically.

Data on pregnancies in female patients and pregnancy outcome (until age 1 month) and AEs in the fetus or newborn infant will be presented in a listing.

Additional data collected regarding medication errors, misuse and abuse of randomized treatment will be presented in listings.

4.6 Other Analyses

All endpoints with time frame ending at year 2 (see Section 1.1.2.3.1) will be summarized descriptively.

4.6.1 Medical history and concomitant illness

Medical history and concomitant illness will be summarized by:

- system organ class and preferred term (to report the diagnosis entered in the “other” categories)
- the pre-defined categories specified on the “Medical History/Concomitant Illness” eCRF page
- the following derived variables:
  - Coronary Heart Disease incl. procedures
  - Peripheral arterial disease incl. procedures
  - Diabetic nephropathy, derived

The derived variables are defined by the categories specified on the “Medical History/Concomitant Illness” eCRF page in the following way:

Coronary Heart Disease incl. procedures

- Stable angina pectoris

- Angina pectoris unstable
- Myocardial infarction
- Coronary artery stenosis
- Percutaneous coronary intervention
- Coronary artery bypass graft

Peripheral arterial disease incl. procedures
- Peripheral arterial disease
- Peripheral revascularization
- Leg amputation

Diabetic nephropathy, derived
- Diabetic nephropathy
- Chronic kidney disease [any sub level]
- Urine albumin/creatinine ratio abnormal [any sub level]

4.6.2 Oral semaglutide dosing

The last dose of oral semaglutide (as collected on the eCRF pages "First Dose" and "Randomized Treatment Medication") for treatment completers will be summarized categorically. In addition, data collected by means of the dosing condition questionnaire (Protocol Section 8.1.4.6) will be summarized categorically except from question 6 ("How long after your last meal did you generally take the pill?") which will be summarized like a continuous variable as described in Section 4.1.

4.6.3 Patient-reported outcomes

Data on Patient Global Impression (PGI) and Clinical Global Impression (CGI) questionnaires (Protocol Sections 8.1.4.3 and 8.1.4.4) will only be summarized descriptively by means of frequency tables.

Item scores for DTSQ (only Item 2 and Item 3) as well as the scores for the Work Limitations Questionnaire (WLQ) and the Work Productivity and Activity Impairment General Health (WPAI-GH) will be analyzed just like the endpoint "DTSQc, Relative treatment satisfaction total score" as described in Section 4.3.1.1. The time frame for the analyses will be year 1. Details on the scorings are provided in Appendix 2 (Section 6.2).

4.6.4 Other variables

The following table provides an overview of other variables not specified as endpoints in the protocol and the corresponding statistical analysis.

Type	Title	Time frame	Unit	Details
Other assessment	Patient achieving HbA_{1c} < 7.0% and ≥5% reduction in body weight (Yes/No)	Year 1	Count of patient(s)	Statistical analyses as specified for binary endpoints in Section 4.3.1.2.
	Change from baseline in eGFR	From baseline to year 1	mL/min/ 1.73m^2	Descriptive summaries (continuous and categorical) for the primary estimand and first exploratory estimand.

Type	Title	Time frame	Unit	Details
				The eGFR will be calculated using the CKD-EPI formula. See Appendix 2 (Section 6.2.1) for details.
	Ratio to baseline in triglycerides	From baseline to year 1	Ratio	Descriptive summary (continuous) for the primary estimand and first exploratory estimand. Geometric mean and coefficient of variation (CV) will be reported instead of arithmetic mean and standard deviation. Baseline values are based on available data within the last 90 days prior to the day of randomization. If value is not available at the required year 1 visit (V3), the closest value ±10 weeks from the year 1 target visit (i.e. week 52) is accepted if available.
	Ratio to baseline in LDL cholesterol	From baseline to year 1	Ratio	
	Ratio to baseline in HDL cholesterol	From baseline to year 1	Ratio	
	Ratio to baseline in Total cholesterol	From baseline to year 1	Ratio	
	Ratio to baseline in UACR	From baseline to year 1	Ratio	
	Change from baseline in systolic blood pressure	From baseline to year 1	mmHg	Descriptive summary (continuous) for the primary estimand and first exploratory estimand.
	Change from baseline in diastolic blood pressure	From baseline to year 1	mmHg	
	Change from baseline in FPG	From baseline to year 1	mg/dL	
	Time to first treatment discontinuation (permanent or temporary)	From date of first dose on study product to date of last dose on study product*	Days	Analyzed by means of a Cox proportional hazards model with treatment as fixed factor. Used as second medication persistence measure in this study.
	Time to permanent treatment discontinuation at year 1	From date of first dose on study product to date of last dose on study product*	Days	

Abbreviations: CKD-EPI = chronic kidney disease – epidemiology collaboration; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; UACR = urine albumin to creatinine ratio.

*Patients having no events at the time of the required year 1 visit (V3) will be censored on the day before the required (planned) year 1 visit (V3).

Descriptive summaries of proportion of patients with intensification of metformin use or use of additional glucose-lowering medications will be provided.

A descriptive summary on patient level of sites will be given based on the eCRF page "Treating physician practice and speciality".

4.7 Interim Analysis

Not applicable.

4.8 Changes to Protocol-planned Analysis

The main analyses were described in the protocol for the study NN9924-4558. However, clarifications, more detailed descriptions of endpoints and analyses are provided in this SAP. The changes from the protocol of NN9924-4558 are summarized below:

- The description of the estimands when used in an analysis in Section 1.1.3 has been slightly modified to avoid confusion.
- The method to handle the convergence issue of analysis model has been mentioned in the primary analysis section.
- All HCRU endpoints are removed as the decision was made to not implement tokenization in this study due to the complexity involved in tokenizing the data and the limited value it would offer for this study.

5 Sample size determination

Please refer to the protocol.

6 Supporting Documentation

6.1 Appendix 1: List of abbreviations

AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
CGI	clinical global impression
CKD-EPI	chronic kidney disease – epidemiology collaboration
CV	coefficient of variation
DPS	data points set
DTSQ	diabetes treatment satisfaction questionnaire
DTSQc	diabetes treatment satisfaction questionnaire, change version
DTSQs	diabetes treatment satisfaction questionnaire, status version
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ETD	estimated treatment difference
E&M	evaluation and management
FAS	full analysis set
FPG	fasting plasma glucose
GFR	glomerular filtration rate
HbA_{1c}	glycosylated hemoglobin A1c
HDL	high-density lipoprotein
HEDIS	healthcare effectiveness data and information set
LDL	low-density lipoprotein

MedDRA	medical dictionary for regulatory activities
PGI	patient global impression
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous
TFL	tables, figures and listings
T2D	type 2 diabetes
UACR	urine albumin to creatinine ratio
WLQ	work limitations questionnaire
WPAI-GH	work productivity and activity impairment general health

6.2 Appendix 2: Definition and calculation of endpoints, assessments and derivations

6.2.1 eGFR

The eGFR will be calculated using the chronic kidney disease – epidemiology collaboration (CKD-EPI) formula.

The formula for eGFR calculation[5] is given in Figure 6-1.

Figure 6-1 Adult GFR estimating equations

ADULT GFR ESTIMATING EQUATIONS

2009 CKD-EPI creatinine equation: $141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ [× 1.018 if female] [× 1.159 if black], where SCr is serum creatinine (in mg/dl), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min is the minimum of SCr/κ or 1, and max is the maximum of SCr/κ or 1.

Equations expressed for specified sex and serum creatinine level

Gender	Serum creatinine	Equation for estimating GFR
Female	⩽0.7 mg/dl (⩽62 µmol/l)	$144 \times (SCr/0.7)^{-0.329} \times 0.993^{Age}$ [× 1.159 if black]
Female	>0.7 mg/dl (>62 µmol/l)	$144 \times (SCr/0.7)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]
Male	⩽0.9 mg/dl (⩽80 µmol/l)	$141 \times (SCr/0.9)^{-0.411} \times 0.993^{Age}$ [× 1.159 if black]
Male	>0.9 mg/dl (>80 µmol/l)	$141 \times (SCr/0.9)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]

6.2.2 DTSQ

The Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) and change version (DTSQc) are used to evaluate patient satisfaction with treatment.

Both questionnaires consist of 8 items, 6 of which (1, and 4 through 8) assess treatment satisfaction. Each item is rated on a 7-point Likert scale. The change version (DTSQc) has the same 8 items as the status version (DTSQs) with a small alteration of the wording of Item 7. Scores from the 6 treatment satisfaction items are summed to a Total Treatment Satisfaction Score, which ranges from 0 (very dissatisfied) to 36 (very satisfied) for the DTSQs and from -18 (much less satisfied) to +18 (much more satisfied) for the DTSQc.

The DTSQs will be completed at randomization (V1.1) and the DTSQc will be completed at the required study visit at year 1 (V3) (and year 2 (V5) for patients in the exploratory phase). Table 6-1 provides an overview of the items in the questionnaires.

The “prefer not to respond” option in the electronic version of the questionnaire should be treated in the same way as missing data[6].

Missing data at instrument level will be handled in the following way. For computing the total treatment satisfaction score consisting of six items, missing data from one item is allowed.

Scoring algorithm:

- Step 1: sum the existing item scores (i.e. either 5 or 6 item scores)
- Step 2: divide this sum by the number of existing item scores
- Step 3: multiply by 6 (the number of items in the total treatment satisfaction scale)

Table 6-1 Overview of items in DTSQs and DTSQc

Item No.	Item text	Response scale DTSQs	Response scale DTSQc
1	How satisfied are you with your current treatment?	6 = very satisfied, 5, 4, 3, 2, 1, 0 = very dissatisfied	3 = much more satisfied now, 2, 1, 0, -1, -2, -3 = much less satisfied now
2	How often have you felt that your blood sugars have been unacceptably high recently?	6 = most of the time, 5, 4, 3, 2, 1, 0 = none of the time	3 = much more of the time now, 2, 1, 0, -1, -2, -3 = much less of the time now
3	How often have you felt that your blood sugars have been unacceptably low recently?	6 = most of the time, 5, 4, 3, 2, 1, 0 = none of the time	3 = much more of the time now, 2, 1, 0, -1, -2, -3 = much less of the time now
4	How convenient have you been finding your treatment to be recently?	6 = very convenient, 5, 4, 3, 2, 1, 0 = very inconvenient	3 = much more convenient now, 2, 1, 0, -1, -2, -3 = much less convenient now
5	How flexible have you been finding your treatment to be recently?	6 = very flexible, 5, 4, 3, 2, 1, 0 = very inflexible	3 = much more flexible now, 2, 1, 0, -1, -2, -3 = much less flexible now
6	How satisfied are you with your understanding of your diabetes?	6 = very satisfied, 5, 4, 3, 2, 1, 0 = very dissatisfied	3 = much more satisfied now, 2, 1, 0, -1, -2, -3 = much less satisfied now
7	DTSQs: Would you recommend this form of treatment to someone else with your kind of diabetes? DTSQc: How likely would you be to recommend your present treatment to someone else with your kind of diabetes?	6 = Yes, I would definitely recommend the treatment, 5, 4, 3, 2, 1, 0 = No, I would definitely not recommend the treatment	3 = much more likely to recommend the treatment now, 2, 1, 0, -1, -2, -3 = much less likely to recommend the treatment now
8	How satisfied would you be to continue with your present form of treatment?	6 = very satisfied, 5, 4, 3, 2, 1, 0 = very dissatisfied	3 = much more satisfied now, 2, 1, 0, -1, -2, -3 = much less satisfied now

An electronic version of the questionnaire has the option “prefer not to respond”.

6.2.3 WPAI-GH Questionnaire

The WPAI-GH questionnaire assesses both absenteeism (i.e., work time missed) and presenteeism (i.e., impairment at work or reduced on-the-job effectiveness) as well as daily activity impairment (e.g., work around the house, shopping, exercising, childcare, studying) attributable to general health.

The WPAI-GH will be administered at randomization (V1.1) and at the required study visit at year 1 (V3) (and year 2 (V5) for patients in the exploratory phase).

Version 2.0 of the questionnaire[7,8] is applied in this study and Table 6-2 provides an overview of the items in the questionnaire. Handling of missing data is described in the reference.

Scoring:

The WPAI yields four types of scores:
1. Absenteeism (work time missed)
2. Presenteeism (impairment at work / reduced on-the-job effectiveness)
3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)

4. Activity Impairment

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes.

Formulas for score derivation (in percentage) are given below.

Absenteeism (work time missed):
Score = (*Item 2* / (*Item 2* + *Item 4*)) * 100

Presenteeism (impairment at work / reduced on-the-job effectiveness):
Score = (*Item 5* /10) * 100

If *Item 4* = 0, score is not applicable, and the score is set to missing.

Work productivity loss (overall work impairment / absenteeism plus presenteeism):
Score = ((*Item 2* / (*Item 2* + *Item 4*)) + ((1 - (*Item 2* / (*Item 2* + *Item 4*))) * (*Item 5* / 10))) * 100

Activity Impairment:
Score = (*Item 6* / 10) * 100

Table 6-2 Overview of items in WPAI-GH questionnaire

Item No.	Item text	Response scale
1	Are you currently employed (working for pay)? If NO, check "NO" and skip to question 6	YES, NO
2	During the past seven days, how many hours did you miss from work because of your health problems? Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.	Free text field to enter hours
3	During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?	Free text field to enter hours
4	During the past seven days, how many hours did you actually work? (If "0", skip to question 6.)	Free text field to enter hours
5	During the past seven days, how much did your health problems affect your productivity while you were working?	0 = Health problems had no effect on my work, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 = Health problems completely prevented me from working
6	During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?	0 = Health problems had no effect on my daily activities, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 = Health problems completely prevented me from doing my daily activities

6.2.4 WLQ

WLQ is a 25-item questionnaire that measures the degree to which health problems interfere with specific aspects of job performance and the productivity impact of these work limitations during the past 2 weeks. The questionnaire consists of 4 domains of work limitation: Time Management (5), Physical Demands (6), Mental/Interpersonal (9), Output Demands (5). The responses are used to calculate a total WLQ index score, converted into an estimate of productivity loss, and compared to "healthy" employee.

The WLQ will be administered at randomization (V1.1) and at the required study visit at year 1 (V3) (and year 2 (V5) for patients in the exploratory phase).

The scoring of the WLQ and handling of missing data is described in the reference[9,10].

6.2.5 Patient achieving individualized HbA_{1c} target per HEDIS criteria (<8.0% if age ≥65 years or with defined comorbidities or otherwise <7.0%)

Defined comorbidities are captured on the "Medical History/Concomitant Illness" eCRF page.

The responder criterion is

- < 8.0% if age ≥65 years or with defined comorbidities as listed below
- < 7.0% if age <65 years and without evidence of any comorbidities as listed below

HEDIS criteria	eCRF
Coronary artery bypass surgery or percutaneous coronary intervention	Percutaneous coronary intervention or Coronary artery bypass graft
Ischemic vascular disease	Stable angina pectoris or Angina pectoris unstable or Coronary artery stenosis or Stroke or Carotid artery stenosis (≥50% stenosis) or Carotid revascularisation or Peripheral arterial disease (atherosclerotic disease) or Peripheral revascularisation
Thoracic Aortic Aneurysm	Thoracic Aortic Aneurysm
Chronic Heart failure	Heart Failure
Prior myocardial infarction	Myocardial infarction
Chronic renal failure / end-stage renal disease	G4 or G5 [Chronic Kidney disease]
Dementia	Dementia
Blindness	Blindness [bilateral or unilateral] or Low vision [one or both eyes]
Lower extremity amputation	Leg amputation (only due to atherosclerosis)

7 References

1. Oster G, Sullivan SD, Dalal MR, Kazemi MR, Rojeski M, Wysham CH, et al. Achieve control: a pragmatic clinical trial of insulin glargine 300 U/mL versus other basal insulins in insulin-naïve patients with type 2 diabetes. Postgrad Med. 2016;128(8):731-9.
2. National Committee for Quality Assurance. Comprehensive Diabetes Care (CDC) [Internet] 2021 [cited 2021 15 Jul].
3. European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, Step 2b (EMA/CHMP/ICH/436221/2017). 30 Aug 2017.
4. Little R, Rubin D. Statistical analysis with missing data. Sons. JW, editor. New York.: John Wiley & Sons. 1987.
5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3(1):1-150.
6. Bradley C. The Diabetes Treatment Satisfaction Questionnaire (DTSQ), Status and Change Versions, User Guidelines. 25 AUG 2021.
7. Reilly Associates. Work Productivity and Activity Impairment Questionnaire [Internet] 2002 [cited 2021].
8. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353-65.
9. Lerner D, Amick BC, Rogers WH, Malspeis S, Bungay K, Cynn D. The Work Limitations Questionnaire. Med Care. 2001;39(1):72-85.
10. Mapi Research Trust. Work Limitations Questionnaire - Scaling and Scoring Version 1.0. 2018.