Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05035082
Sponsor trial ID:	NN9924-4558
Official title of study:	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.
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Protocol

Protocol title: 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

Universal Trial Number: U1111-1253-2577

Redacted protocol
includes redaction of company confidential information.

Study phase: IV

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

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Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in counties and/or site
Protocol version 5.0	18 February 2025	All
Protocol version 4.0	27 March 2023	All
Protocol version 3.0	21 December 2022	All
Protocol version 2.0	31 May 2022	All
Original protocol version 1.0	07 June 2021	All

Overall rationale for preparing protocol, version 5.0:

This amendment is created to remove the administrative claims data and to revise the CGI COA scale from a 7-point scale to a 5-point scale. Changes to the content of the protocol are presented in greater detail in the table below.

Section # and name	Description of change	Brief rationale
Section 8.1.4.4 Clinician Global Impression of Disease Severity and Clinician Global Impression of Change	The CGI-C scale has been revised to a 5-point scale ranging from 1 (normal) to 5 (very severe).	The CGI-C scale should have been the 7-point scale ranging from 1 (very much better) to 7 (very much worse or very severe). However, by mistake the CGI-C scale that was used in the study was the 5-point scale ranging from 1 (Normal) to 5 (very severe).
Section 8.1.5 Administrative claims data	The section has been deleted.	The section 'Administrative Claims Data' is 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.

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Protocol Attachment I Global list of key staff and relevant departments and key suppliers of clinical relevance

1 Protocol summary

1.1 Synopsis

This is an interventional, multi-center, randomized, open-label, parallel-group, active comparator-controlled pragmatic study comparing oral semaglutide versus one other oral glucose-lowering medication both added to metformin in routine primary care clinical practice, in adult patients with type 2 diabetes (T2D) in which further intensification with an additional oral glucose-lowering medication is indicated at the discretion of the treatment provider.

Rationale

The present pragmatic study serves the purpose of evaluating the effectiveness of oral semaglutide as compared with commercially available oral glucose-lowering therapies added to metformin monotherapy in a real-world population with T2D.

The study will be conducted in a primary care practice setting within one or more healthcare systems with wide eligibility criteria thereby increasing generalizability while balancing the internal validity of an explanatory randomized controlled study. This will generate data to complement the findings from the PIONEER phase 3a program with focus on the early use of oral semaglutide in a routine practice setting. Taken together, the present pragmatic study will provide important evidence in the routine clinical practice for decision making by clinicians, payers and policy makers.

Objectives and endpoints

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 T2D on metformin monotherapy in the primary care setting and routine clinical practice.

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

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

The primary endpoint is:

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

All primary and secondary endpoints will employ the primary estimand. 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.

Overall design

This is multi-center, randomized, open-label, parallel-group, active comparator-controlled pragmatic study comparing oral semaglutide versus one other oral glucose-lowering medication both added to metformin in routine primary care clinical practice, in adult patients with T2D in which further intensification with an additional oral glucose-lowering medication is indicated at the discretion of the treatment provider.

The clinical investigators participating in this study may be part of a health system or individual practicing physicians that are treating patients.

Within the health system the investigator will manage/facilitate the identification and consenting of potential patients based on evaluation of patients' medical data meeting eligibility criteria. The treatment provider will confirm patients' eligibility and need for intensification at their routine care visit and will prescribe an oral glucose-lowering medication based on the randomized treatment assignment. In order to have a broad and representative population reach, the treatment provider does not have to also be an investigator. Throughout the study period the treatment provider will treat the patients based on their clinical judgement and routine practice and document all decisions and assessment results in the patients' medical chart.

The investigator and/or study staff will transcribe the study required data for each patient enrolled from their medical chart into the electronic case report form (eCRF).

At the individual practitioner site the role of the investigator and treatment provider may be fulfilled by a single individual, but the operational aspects of the study will be the same as described for the treatment provider within the health-system. As the treatment provider they will treat the patients based on their clinical judgement and routine practice and document all decisions and assessment results in the patients' medical chart. The study staff will transcribe the study required data for each patient enrolled from their medical chart into the electronic case report form (eCRF).

The study will employ selected safety collection. The investigator will be responsible for reporting of safety information within the reporting timelines, and of contacting the patient for any required follow-up.

The study consists of: a visit for informed consent, patient level randomization, and treatment initiation (may be split in a screening and a randomization visit), a number of intermediate visits depending on the local clinical practice; a required visit at the end of year 1. No follow-up visits are planned.

A subgroup, consisting only of patients enrolled prior to protocol version 3.0, will continue in an exploratory phase (year 2, see section 4.1 and Figure 4-1). For these patients, in addition to the above, there will be a number of intermediate visits depending on the local clinical practice; and lastly a required end of treatment visit at the end of the second year. No follow-up visits are planned.

Randomized treatments

The medications used in this study are:

- Rybelsus®, oral semaglutide, including all commercially available dose options, Novo Nordisk A/S, Denmark. Rybelsus®, oral semaglutide, should be used in accordance with US approved prescribing information.
- Oral glucose-lowering medications should be used in accordance with approved US prescribing information and local clinical practice and guidelines for the individual drugs. Medicinal products with more than one active substance (i.e. fixed-dose combination products) are not allowed as randomized treatment unless metformin, at the same dose level prior to intensification, is a component. Patients can only intensify treatment with one agent. The oral glucose-lowering medications used in this study should be commercially available.

Treatment groups and duration

To preserve the real-world nature of the study, the patient experience will be as close to routine care as possible. The treatment providers are the patients' own physicians who may make treatment adjustments according to their clinical judgement and prescribing information. The treatment provider can make repeat prescriptions of randomized treatment as usual, which are collected by patients from their pharmacy. These patients must, prior to being randomized, be willing to intensify with an additional oral glucose-lowering medication including oral semaglutide.

Prior to randomization the treatment provider will select the other glucose-lowering mediation that will be prescribed in the event the patient is not randomized to oral semaglutide. After randomization, patients will receive either commercially available oral semaglutide or one of any other commercially available oral glucose-lowering medication according to local clinical practice at the discretion of the treatment provider.

Patients in the oral semaglutide group will initiate treatment with oral semaglutide according to the approved prescribing information. The treatment provider will determine the timing of dose escalation and intended maintenance dose of oral semaglutide, as well as changes to the maintenance dose thereafter.

Patients in the one other oral glucose-lowering medication group (comparator group) will be initiated with commercially available oral glucose-lowering medication at the discretion of the treatment provider according to approved prescribing information and, if relevant for the specific glucose-lowering medication, escalated at the discretion of the treatment provider.

In both treatment groups add-on, discontinuation or dose modification of oral or injectable additional glucose-lowering medication, excluding s.c. and oral semaglutide, during the study is allowed at the discretion of the treatment provider.

The randomized treatments will be handled and dispensed by the patients' pharmacy per their preference and health plan benefits in order for the study to remain as close to real world as possible. Novo Nordisk A/S will be providing an out-of-pocket maximum as part of the study, for randomized treatment for the duration of the study. This is to reduce the impact of any differential in out-of-pocket costs between the treatment groups.

Number of patients

Approximately 1,388 patients will be screened to achieve 1,262 patients randomly assigned to oral semaglutide or one other oral glucose-lowering-medication.

Patient characteristics

The patients will be male and/or female patients with T2D aged ≥ 18 years at inclusion who meet the following key inclusion criteria and none of the following key exclusion criteria.

Key inclusion criteria:

- Treatment with metformin as monotherapy prior to eligibility assessment that has failed to result in adequate glycemic control at the discretion of the investigator or treatment provider. However, prior short-term treatment with an oral glucose lowering agent or insulin for up to 14 consecutive days in addition to metformin is allowed if discontinued prior to screening.
- Current member of a health plan which includes pharmacy benefits.
- $HbA_{1c} \geq$ 7% within last 90 days prior to the day of screening or to be taken before randomization.
- Further intensification with an additional glucose-lowering oral agent including oral semaglutide is indicated according to approved prescribing information to achieve glycemic target at the discretion of the treatment provider.

Key exclusion criteria:

- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using contraception.
- Any disorder which in the investigator's or treatment provider's opinion might jeopardize patient's safety.

Data monitoring committee

This study will not have a data monitoring committee however, data will be monitored on an ongoing basis by the Novo Nordisk study team via routine data management reports.

1.2 Flowchart

Procedure	Screening	Randomization visit	Intermediate visits	Required Year 1 visit	Intermediate visits	Required Year 2 visit
					EXPLORATORY PHASE	
Visit (V)	V1	V1.1	V2.X	V3	V4.X	V5
Time of visits (weeks)[a]	Up to -4	-	Up to 46	52±6	58-98	104±6
Visit window [Days interval]	[-28 to -1]	[0]	[1-321]	[322-406]	[407-685]	[686-770]
PATIENT AND TREATMENT RELATED ASSESSMENTS[a,b]						
Treatment provider practice and specialty[c]		X				
Informed consent[d]	X					
Choice of oral glucose-lowering agent[e] and individualized HbA_{1c} target[f]		X				
Randomized treatment medication[g]		X	X	X	X	X
Randomization		X				
In/Exclusion criteria	X	X				
Demography and tobacco use		X				
Medical and diabetes history		X				
Concomitant medication[g,h]		X	X	X	X	X

Procedure	Screening	Randomization visit	Intermediate visits	Required Year 1 visit	Intermediate visits	Required Year 2 visit
EFFECTIVENESS AND SAFETY RELATED ASSESSMENTS, AND QUESTIONNAIRES						
Body weight		X	X	X	X	X
Height		X				
Systolic blood pressure / Diastolic blood pressure		X	X	X	X	X
FPG		X		X		X
HbA_{1c}		X[j]	X	X[i]	X	X[i]
Creatinine		X[j]		X[i]		X[i]
UACR		X[j]		X[i]		X[i]
Lipids-triglycerides/total cholesterol/HDL and LDL		X[j]		X[i]		X[i]
SAE´s, pregnancies, and AE´s leading to discontinuation of randomized treatment, AEs related to COVID-19 and pregnancy outcome [until age 1 month] and AEs in the fetus or new-born infant		X	X	X	X	X
Diabetes Treatment Satisfaction Questionnaire (DTSQ)[j]		X		X		X
Patient Global Impression (PGI)[k]		X		X		X
Clinician Global Impression questionnaire (CGI)[k]		X		X		X
Work Productivity and Activity Impairment (WPAI)		X		X		X
Work Limitations Questionnaire (WLQ-GH)		X		X		X

Procedure	Screening	Randomization visit	Intermediate visits	Required Year 1 visit	Intermediate visits	Required Year 2 visit
Dosing conditions[l]				X		X
END OF STUDY						
End of study				X		X

Abbreviations: V=visit; HbA_{1c}=glycated hemoglobin A1c; PRO=patient reported outcome; SAE=serious adverse event; AE= adverse event.

[a] Intermediate visits will follow standard care frequency and any available data will be entered in the eCRF.

[b] Assessments at required study visits will be collected in eCRF.

[c] Includes information of type of treatment provider and setting.

[d] Informed consent must be obtained before any study-related activities.

[e] Choice of oral agent for intensification if not randomized to Rybelsus®.

[f] To be established prior to randomization and knowledge of treatment assignment.

[g] Changes to glucose lowering medication will also be followed up at quarterly phone calls to the patient by the investigator.

[h] Concomitant medication related to diabetes, CV risk, obesity, thyroid and COVID-19 study participation only.

[i] If value is not available at the dedicated visits at year 1 (V3) (and year 2 (V5) for patients in the exploratory phase), the closest HbA_{1c}, creatinine and UACR value and categorization recorded ± 10 weeks is accepted if available.

[j] The value is based on available data within the last 90 days prior to the day of randomization.

[k] Status versions of the questionnaires at baseline, and change version at year 1 visit (and year 2 visit, for patients in the exploratory phase).

[l] Parameters associated with how Rybelsus® was taken will be collected in a patient questionnaire for the patients randomized to Rybelsus®. This includes amount of fluid taken with the tablet and time from dosing to next meal or drink.

2 Introduction

2.1 Study rationale

The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) position statement recommends a patient-centered approach to the selection of pharmacological treatment for type 2 diabetes (T2D), including assessment of key patient characteristics such as comorbidities (i.e. atherosclerotic cardiovascular disease [ASCVD], chronic kidney disease [CKD] and heart failure [HF]) and considerations on individualized glycated hemoglobin A1c (HbA_{1c}) target, hypoglycemia risk, impact on body weight, side effects, costs and patient preferences.[1]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended for management of hyperglycemia in T2D following first line therapy with metformin and the ADA/EASD consensus report highlights and recommends the use of GLP-1 RAs and/or SGLT-2i in appropriate high-risk individuals to reduce major cardiovascular events (MACE), hospitalization for heart failure, cardiovascular death or chronic kidney disease progression to be considered independently of baseline HbA_{1c} or individualized target.[1, 2]

Oral semaglutide (Rybelsus®), a novel GLP-1 analog, is the first peptide-based anti-diabetic therapy available for oral administration. Based on a comprehensive global clinical development program (PIONEER), once-daily oral semaglutide was recently approved as an adjunct to diet and exercise to improve glycemic control in adults with T2D.

Traditional randomized clinical studies (RCSs) are used to initially assess the safety and efficacy of a new therapy and randomizes a selected patient population in a highly controlled setting with the aim of increasing internal validity and decreasing the risk of bias. Traditional RCSs are thus suited and needed to establish causal inference and are the foundation for regulatory decision-making, such as approval of new therapies. However, due to the highly controlled setting of traditional RCSs and a selected population, the generalizability of these to community practice decision-making can be challenging if the patients treated in routine clinical practice differ from those in the study. The overall care patterns and quality may differ from that received in the study or therapeutic adherence or persistence in practice varies markedly from that seen in the study. In landmark clinical studies the majority of the general patient population is not fulfilling study eligibility criteria [2-4] and there generally exists a treatment effect gap between effects observed in RCSs compared to the effects observed in routine clinical practice (primarily due to poor medication adherence).[5]

Pragmatic studies are designed and conducted to reflect patient outcomes and to investigate how a product is used and performs in routine clinical practice. This type of study typically compares two or more treatment strategies that are directly relevant to clinical care and strive to assess the comparative effectiveness of the interventions in routine clinical practice. These studies use broad eligibility criteria and recruit patients from a variety of clinical practice settings to ensure the inclusion of a population resembling all types of patients whose future care will be influenced by the results. Such studies are increasingly important to provide information about treatment outcome to inform clinicians and patients, and potentially support health systems in appropriate population-based treatment guidance and prioritization.

The present pragmatic study serves the purpose of evaluating the comparative effectiveness of oral semaglutide as compared with commercially available oral glucose-lowering therapies added to metformin monotherapy in a broad clinic population. The study will be conducted in a primary care practice setting in a number of separate practices and within one or more healthcare systems thereby increasing generalizability while balancing the internal validity of an explanatory randomized controlled study. This will generate data to complement the findings from the PIONEER phase 3a program with focus on the early use of oral semaglutide in a real-life setting. Taken together, the present pragmatic study will provide important evidence in the routine clinical practice for decision making by clinicians, payers and policy makers.

2.2 Background

The PIONEER program was a comprehensive clinical program including 10 phase 3a studies comprising 9,543 patients with T2D. The program confirmed a favorable benefits/risk profile of oral semaglutide in a broad population of patients with T2D, including drug-naïve and insulin-requiring patients and patients with micro- and macrovascular diabetes complications. Clinically relevant and sustained improvements in glycemic control and reductions in body weight were demonstrated, and the safety and tolerability profiles of oral semaglutide were consistent with those of other GLP-1 RAs.[5]

In the PIONEER program, oral semaglutide overall showed superior results against almost all comparators with clinically relevant reductions in HbA_{1c} and on body weight. Oral semaglutide 14 mg was non-inferior in glycemic control and showed superiority on body weight compared with liraglutide 1.8 mg. Oral semaglutide 14 mg confirmed superiority on HbA_{1c} but did not confirm superiority on body weight vs empagliflozin 25 mg. Oral semaglutide 7 mg and 14 mg confirmed superiority on HbA_{1c} and body weight vs sitagliptin 100 mg. In addition, in a pre-approval cardiovascular outcomes trial (CVOT), oral semaglutide was non-inferior on major adverse cardiovascular events (MACE) and showed a non-significant risk reduction on MACE in patients with T2D at high risk of cardiovascular (CV) events compared with placebo. The overall safety profile of oral semaglutide was consistent with semaglutide s.c. and the well-established GLP-1 RA class safety profile.[6, 7]

2.3 Benefit risk assessment

A summary of the known and potential risks and benefits for oral semaglutide (Rybelsus®) and one other oral glucose-lowering medication that the patient can be randomized to is described in respective local prescribing information. For each participating patient a benefit risk assessment is done according to regular clinical practice and current approved local prescribing information by the treatment provider as part of the inclusion into the study.

It has been assessed that there is no increased risk of COVID-19 infection in relation to participation in REALYSE. There is also no perceived risk in relation to data capturing and risk of missing data in relation to COVID-19 due to the wide visit windows. The participation and visits will follow regular clinical practice and include patients deemed relevant to intensify treatment by the treatment provider. Additionally, the choice of treatments is at the discretion of the treatment provider and based on local prescribing information.

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objectives and estimands

3.1.1 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 T2D on metformin monotherapy in the primary care setting and routine clinical practice.

3.1.2 Secondary objectives

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]

3.2 Primary, secondary and exploratory endpoints

3.2.1 Primary endpoint

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

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

3.2.2 Secondary endpoints

3.2.2.1 Supportive secondary endpoints

Effectiveness endpoints

Endpoint title	Time frame	Unit
Patient achieving HbA_{1c} < 7.0% (Yes /No)	Year 1	Count of patient(s)

Endpoint title	Time frame	Unit
Patient achieving $HbA_{1c} \leq 6.5\%$ (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 [8, 9] (<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.

3.2.3 Exploratory endpoints

3.2.3.1 Exploratory endpoints: Year 1

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[redacted]

CCI

[redacted]

CCI

[redacted]

3.2.3.2 Exploratory endpoints: Exploratory phase subgroup only

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[redacted]

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[redacted]

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[redacted]

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[redacted]

3.3 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)[10] are specified for the three estimands in Table 3-1 below.

The following rules will be applied for the intercurrent events mentioned in Table 3-1:

- 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 3-1 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

Estimand category	Estimand				
	Treatment condition	**Variable / Endpoint**	**Population of interest**	**Intercurrent events and strategy**	**Population-level summary measure**
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

Primary estimand

All primary and secondary endpoints will employ the primary estimand.

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 estimands

An exploratory estimand will be employed for the CCI [redacted], secondary endpoints, 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.

4 Study design

4.1 Overall design

This is an interventional randomized, open-label, parallel-group, active comparator-controlled two-armed multi-center pragmatic study in a primary care setting. Primary care is defined as a practice that "serves as the patient's first point of entry in to the health care system and as the continuing focal point for all needed health care services".[11]

The conduct and operations of the study will be managed by the investigator and study team within the health system or at the primary care practice. Within the health system and practice the treatment providers will provide diabetes care to the patients enrolled in the study. The treatment providers will follow their routine care and medical judgement to treat the patients. They will record the assessments and observations in the patients' medical chart. The investigator and study staff will extract the study required data from the patients charts or call the patient to inquire about status of medication. Study relevant data will be transcribed into the eCRF.

Following the treatment provider's decision to intensify therapy with an additional oral glucose-lowering agent, patients on metformin monotherapy will be randomized 1:1 to receive either oral semaglutide or one other oral glucose-lowering medication with no stratification. The patient will have been found eligible for treatment with oral semaglutide and at least one other oral glucose-lowering drug by the treatment provider prior to randomization. Eligibility for the study is assessed using inclusion and exclusion criteria as defined in Sections 5.1 and 5.2.

To ensure that the treatment practice is as close to real world as possible in both treatment groups, all commercially available oral glucose-lowering medications are allowed as randomized treatment in the one other oral glucose-lowering medication treatment group.

Except for semaglutide, oral and s.c. all other oral and injectable glucose-lowering treatments are allowed as additional (subsequent) glucose-lowering treatment in both treatment groups at the treatment providers´ discretion. This exception is to avoid the bias of comparing semaglutide in different formulations.

Total study duration for the individual patient will be approximately 1 year. No follow-up visits are planned.

However, a subgroup, consisting only of patients enrolled prior to protocol version 3.0, will continue in an exploratory phase (year 2). This is due to a protocol amendment (from protocol version 2.0 to 3.0) reducing the study duration for each patient from 2 years to 1 year. This was done to ensure study completion within business critical timelines with sufficient number of patients for securing adequate power to analyze the primary endpoint.

The study consists of:

- a visit for informed consent, patient level randomization, and treatment initiation (may be split in a screening and a randomization visit).
- a number of intermediate visits depending on the local clinical practice.
- a required visit at the end of the year 1.

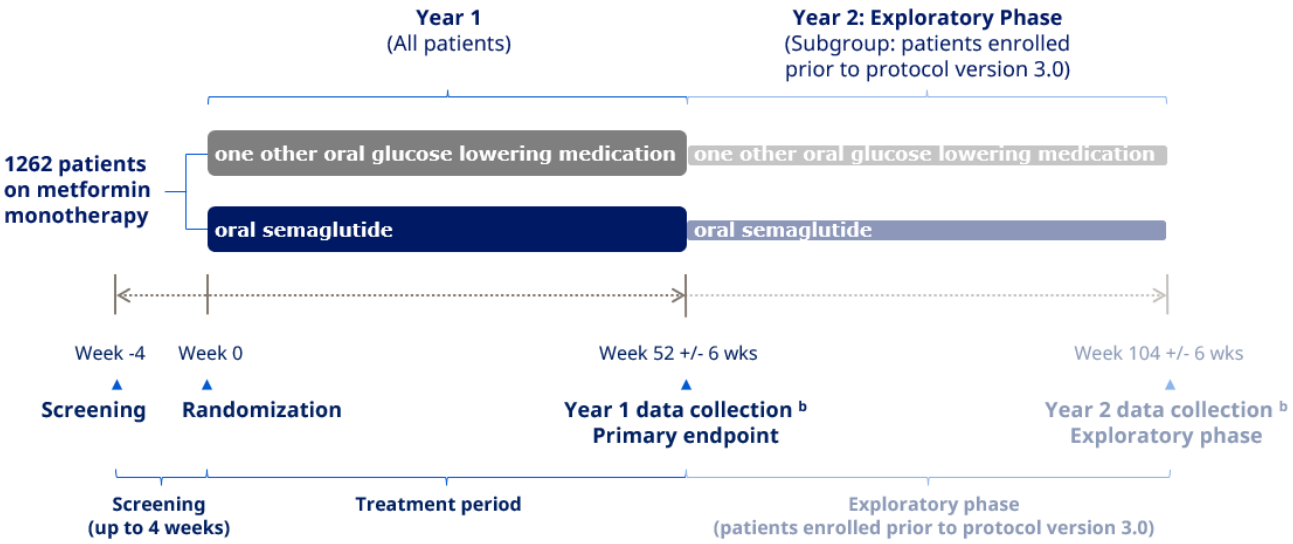
Additionally, for the subgroup continuing in the exploratory phase (year 2), there will be:

- a number of intermediate visits depending on the local clinical practice.
- a required end of treatment visit at the end of the second year.

All visits can be converted to virtual visits as deemed appropriate for the safety and preference of the patient and in accordance with local clinical practice.

A schematic of the study design is shown in Figure 4-1.

Figure 4-1 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.

4.1.1 Data collection

Data collection will be a mix of primary data collection and secondary use of data with data from a variety of sources:

1. Electronic Health Record systems that are maintained by the health care systems and are used to deliver care. Electronic Health Records (EHR) is an individual patient record contained within the EHR system. A typical individual EHR may include a patient's medical history, diagnoses, treatment plans, immunization dates, allergies, radiology images, pharmacy records, and laboratory and test results.[12]
2. Patient survey and questionnaires will be used to capture data on PRO's and treatment satisfaction.
3. Administrative claims data captured by payer partner to estimate health care resources utilization.
4. Follow up phone calls by investigator to patients quarterly primarily with the intention to capture changes to glucose lowering medications.

4.2 Scientific rationale for study design

To evaluate the effectiveness of oral semaglutide as compared to one other oral glucose-lowering medications in a primary care setting reflecting routine clinical practice, randomization was included to reduce selection bias and ensure comparable patient populations in the two treatment groups. To reflect routine primary care practice, the study will be conducted in collaboration with individual primary care physicians in their routine clinical care practices and several health systems within their network of primary care physicians treating patients according to local guidelines and only including patients the treatment providers deem relevant for intensification with an oral glucose-lowering agent.

4.2.1 Patient input to design

Input to study design and operational setup has been discussed and received from a patient representative before finalizing the protocol.

4.3 Justification for dose

The treatment providers will prescribe the randomized treatment and instruct the patients on dosing based on the prescribing information, local practice and their clinical judgement. They will also instruct the patients on all other treatments/medications according to local practice and own medical judgement.

4.4 End of study definition

A study completer is defined as a patient who attends, or is in contact with the site, at the patient's last scheduled visit.

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

The primary completion date (PCD) is the last assessment of the primary endpoint and is for this study last patient first visit/treatment (LPFV/LPFT) + 52 weeks, corresponding to visit 3 (V3). If the last patient is withdrawn early, the PCD is considered the date when the last patient would have completed visit 3 (V3). The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

5 Study population

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

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

5.1 Inclusion criteria

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

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. Type 2 diabetes mellitus diagnosis.
3. Male or female, age ≥ 18 years at the time of signing informed consent.
4. Treatment with metformin as monotherapy prior to eligibility assessment that has failed to result in adequate glycemic control at the discretion of the investigator or treatment provider. However, prior short-term treatment with an oral glucose lowering agent or insulin for up to 14 consecutive days in addition to metformin is allowed if discontinued prior to screening.
5. Current member of a health plan which includes pharmacy benefits.
6. HbA_{1c}≥ 7% within last 90 days prior to the day of screening or to be taken before randomization.
7. Further intensification with an additional glucose-lowering oral agent including oral semaglutide is indicated according to approved prescribing information to achieve glycemic target at the discretion of the treatment provider.

5.2 Exclusion criteria

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

1. Previous participation in this study. Participation is defined as randomization.
2. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using contraception.
3. Participation in any interventional clinical study of an approved or non-approved investigational medicinal product within 30 days before screening*.

   *Simultaneous participation in a study with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening.
4. Any disorder which in the investigator's or treatment provider's opinion might jeopardize patient's safety.

5.3 Lifestyle considerations

No specific lifestyle modifications and interventions will be implemented as part of this study.

5.4 Screen failures

A screen failure occurs when a patient who consents to participate in the clinical study is not subsequently eligible for participation according to inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, and eligibility criteria.

A screen failure session must be made in the interactive web response system (IWRS).

Individuals who do not meet the criteria for participation in this study may be rescreened. Individuals who are rescreened are required to sign a new informed consent form and provided with a new patient ID. A new screening session must be made in the IWRS.

6 Treatments and concomitant therapy

6.1 Treatments administered

To preserve the real-world nature of the study, the patient experience will be as close to routine care as possible. The treatment provider will be one of the patient's own primary care practice physicians, who is managing the patient's diabetes and may make treatment adjustments according to their clinical judgement. The treatment provider will prescribe the study medication based on the randomized assignment and the prescription will be filled by a pharmacy. The treatment provider can make repeat prescriptions of the randomized treatment as usual, which are collected by patients from the pharmacy of their choice.

Patients will be randomized to:

- oral semaglutide (Rybelsus®) *or*
- one other commercially available oral glucose-lowering agent.

For patients randomized to receive other treatment than Rybelsus®, the treatment provider can switch between specific drugs within the same class.

The oral glucose-lowering drug classes anticipated to be included as randomized treatment in this study are the commercially available options (listed in alphabetic order):

- Alpha-glucosidase inhibitors
- Dipeptidyl peptidase 4 (DPP-4) inhibitors
- Meglitinides
- Sodium-glucose co-transporter 2 (SGLT-2) inhibitors
- Sulfonylureas
- Thiazolidinediones
- Other

Treatment details will be recorded in the eCRF. All treatments should be used in accordance with local clinical practice and guidelines and prescribing information. The patient will be provided instructions per routine practice. Dosage and any additional details of the treatment should be captured in the eCRF for each visit. Changes to glucose lowering medication will also be followed up at quarterly phone calls to the patient by the investigator.

Additional glucose-lowering medication is allowed after randomization and is described in Section 6.8.

Randomized treatment and dose as prescribed by treatment provider and patients' adherence to the treatment should be recorded in the eCRF for each visit. In addition, dates for dose changes as well as reasons for dose change including treatment pauses and discontinuations as described in Sections 6.5 and 7.1 should be collected in the eCRF.

6.2 Co-pay assistance

The randomized treatment will be handled and dispensed by a pharmacy per the patient's preference and health plan benefits for the study to remain as close to real world as possible. Novo Nordisk A/S will ensure full reimbursement for the randomized treatment. This is to remove potential

impact of out-of-pocket costs between the treatment groups. Co-pay assistance will only apply to the randomized treatment as defined above (i.e., not to any subsequent add-on treatment or treatment changes outside the randomized treatment definition). Because patients can start and stop randomized treatment throughout the study (please refer to Section 7.1), co-pay assistance may also start and stop throughout the study. For the duration of the study, any time a patient is "on randomized treatment" they will receive co-pay assistance, and any time a patient is "off randomized treatment" they will not receive co-pay assistance.

6.3 Measures to minimize bias: Randomization and blinding

This is an open-label study. Randomization will be included to reduce selection bias and ensure comparable patient populations in the two treatment groups.

The treatment provider will decide which treatment the patient should receive if randomized to the "one other oral glucose-lowering medication treatment group" before obtaining the randomized treatment assignment.

All patients will be screened and centrally randomized using an IWRS and assigned to the next available treatment according to the randomization schedule.

6.4 Treatment compliance

Patients' adherence to randomized treatment will be monitored by the study staff through review of the medical records. The treatment provider should support compliance to randomized treatment as he/she does for all other treatments as part of regular clinical practice.

6.5 Dose modification

The dose of the randomized treatment can be modified during the study as per the treatment provider's discretion. All changes to the dose of the randomized treatment should be recorded in the eCRF.

6.6 Continued access to treatment after the end of the study

At the end of the study patients can continue their randomized treatments at the discretion of the treatment provider but co-pay assistance will be discontinued.

6.7 Treatment of overdose

There is no specific antidote for overdose with oral semaglutide. Limited data are available with regard to overdose in patients treated with oral semaglutide. Based on data from treatment with semaglutide the most commonly reported adverse reaction was nausea and all patients recovered without complications.

In the event of overdose, appropriate supportive treatment should be initiated according to the patients' clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of oral semaglutide of approximately one week.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse. Refer to Section 8.3 and Appendix 3 (Section 10.3.3) for further details.

Decisions regarding dose interruptions or modifications will be made by the treatment provider based on the clinical evaluation of the patient. For more information on overdose, also consult the current version of the Rybelsus® prescribing information.

6.8 Concomitant medication

Metformin is considered background medication. Patients may discontinue or change the pre-study dose and frequency of metformin after randomization. This should be captured as concomitant medication changes in the eCRF. Metformin will not be provided nor reimbursed by Novo Nordisk.

Except for all formulations of semaglutide, all other glucose-lowering treatments are allowed as additional glucose-lowering treatment in both treatment groups during the study at the treatment provider's discretion. Such treatments should be recorded in the eCRF with:

- Trade name or generic name
- Indication
- Dose
- Dates of administration including start and stop date

Any medication for obesity, related to cardiovascular risk (e.g. lipid-lowering and antihypertensive medications), hypothyroidism (levothyroxine) or related to participation in a COVID-19 treatment or prevention study that the patient is receiving at the time of the randomization or starts receiving during the study should be recorded in the eCRF along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates

If a change is due to an AE, then this must be reported according to Section 8.3. Any changes in concomitant medication should be recorded in the eCRF.

7 Discontinuation of randomized treatment and patient discontinuation

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

7.1 Discontinuation of randomized treatments

Randomized treatment may be discontinued or paused at any time during the study at the discretion of the treatment provider for safety, behavioral, compliance or administrative reasons.

A patient can stop or start randomized treatment throughout the study; therefore, a patient's randomized treatment discontinuation status can change throughout the duration of the study. At any time during the duration of the study, if a patient is not taking randomized treatment as defined, they will be considered "off randomized treatment". Conversely, at any time during the duration of the study, if a patient is taking randomized treatment, they will be considered "on randomized treatment", regardless of prior randomized treatment discontinuations. Stop and start dates of taking the randomized treatment and reasons for changes (Dose escalation per label; Suboptimal effect/lack of efficacy; Change in treatment strategy; Unacceptable GI intolerability; Side effect(s) other than GI; Pregnancy; Intentions to become pregnant; Change in reimbursement status; Patient preference; Unknown or Other) should be recorded in the eCRF.

The randomized treatment must be discontinued if any of the following applies for the patient:
1. Pregnancy
2. Intention of becoming pregnant
3. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study (except studies to prevent or treat COVID-19)
4. Other reasons according to prescribing information (such as pancreatitis for Rybelsus®)

If a participating patient becomes pregnant, the treatment provider will review the patient's antidiabetic treatment regimen and make any changes necessary according to standard care of patients with T2D during pregnancy. Semaglutide will be discontinued and will not be restarted unless the patient is no longer pregnant or breast-feeding. All randomized treatment co-pay assistance will held while randomized treatment is paused or terminated.

If the treatment provider or patient decides to discontinue randomized treatment during the study the patient should continue in the study off-treatment but complete the visit schedules and procedures.

7.2 Patient withdrawal from the study

A patient may withdraw consent at any time at his/her own request. If a patient 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.

Although a patient 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 patient's rights. Where

the reasons are obtained, the primary reason for withdrawal must be specified in the end of study form in the eCRF.

If a patient withdraws consent or is withdrawn by the investigator, he/she will not be replaced.

7.3 Lost to follow-up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and continues to be unreachable by the investigator or treatment provider's office.

The following actions must be taken if a patient fails to return to the treatment provider's office for a required visit:

- The investigator or treatment provider's office must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining their routine care visits per the schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator, treatment provider, or designee must make reasonable effort to regain contact with the patient (where possible, at least three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of `lost to follow-up'.

8 Study assessments and procedures

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

Informed consent must be obtained before any study-related activity (i.e. randomization); see Appendix 1 (Section 10.1.3).

All screening evaluations must be completed and reviewed by the clinical investigator to confirm that potential patients meet all the inclusion criteria and none of the exclusion criteria.

The investigator will maintain a screening log to record the details of all patients considered and consented to confirm eligibility or record reason for the screen failure, as applicable.

Adherence to the study design requirements, including those specified in the flowchart, is essential and required for the study conduct. Centralized monitoring by the investigator's study staff will be performed to ensure that the patients participate in a required visit at year 1 (V3) (and year 2 (V5) for patients in the exploratory phase).

Enrollment procedure

To preserve the real-world nature of the study, patients will be approached by the investigator (or delegate) for potential enrolment into the study when they have a planned visit with their treatment provider as part of their standard care.

Informed consent will be obtained prior to any study-related activities. At the routine clinical visit the treatment provider will confirm that the patient does not meet any exclusion criteria and make the determination that a patient has inadequate glycemic control on metformin antidiabetic monotherapy, and the subsequent decision to intensify treatment with an additional oral glucose-lowering medication, including oral semaglutide or another oral agent according to approved local prescribing information. The treatment provider will set and document an individualized HbA_{1c} target for patients as well as document the choice (specific drug) of the one other oral glucose-lowering medication if not randomized to oral semaglutide. This will be done prior to randomization based on their clinical judgement and knowledge of the patient.

Following confirmation of inclusion/exclusion criteria, patients will be randomized to either oral semaglutide or one other oral glucose-lowering medication via an IWRS.

8.1 Efficacy assessments

Most efficacy assessments to be recorded in this study are to be based on information already available in the patient's medical records including clinical measures and blood and urine samples. Hence, these data described below is only to be recorded if available and applicable according to local clinical practice.

8.1.1 Body weight

International diabetes guidelines recommend that the Body Mass Index (BMI) should be calculated and documented in the medical record at each patient encounter.[13]

Body weight must be measured and recorded in the eCRF in pounds (lb), with one decimal at each visit. The date and results of the most recent assessment will be recorded at every visit. Self-reported data from virtual visits is acceptable.

8.1.2 Blood pressure

The date and results of the most recent assessment of systolic and diastolic blood pressure (mmHg) should be recorded in the eCRF at every visit.

8.1.3 Blood and urine sampling

8.1.3.1 HbA_{1c} and FPG

The baseline HbA_{1c} will be the patient's most recent HbA_{1c} within 90 days of randomization. HbA_{1c} and fasting plasma glucose (FPG) measurements should be recorded with one decimal place in the eCRF in relation with a relevant visit.

In order to ensure data collection for the primary endpoint, the treatment provider should measure HbA_{1c} in all patients who attend year 1 visit (V3) (and year 2 (V5) for patients in the exploratory phase). The data can be obtained from a point of care test or an accredited clinical laboratory. The international diabetes guidelines recommend to perform the HbA_{1c} test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control) and to perform the HbA_{1c} test quarterly in patients whose therapy has changed or who are not meeting glycemic goals.[14] The date and results of the most recent test will be recorded at every visit.

8.1.3.2 Lipids, creatinine and urinary albumin-to-creatinine ratio

Lipids, serum creatinine and urinary albumin-to-creatinine ratio (UACR) measurements should be recorded in the eCRF if they were collected. The eGFR will be calculated using the chronic kidney disease – epidemiology collaboration (CKD-EPI) formula.[15] The date and results of the most recent test will be recorded.

Lipids, creatinine and UACR are only to be recorded at randomization (V1.1) and year 1 (V3) (and year 2 (V5) for patients in the exploratory phase).

8.1.4 PROs and treatment satisfaction questionnaires

All questionnaires will be administered electronically directly to the patient or the treatment provider. If the patient or treatment provider is unable to complete the questionnaire electronically, the will be provided a paper version.

8.1.4.1 Diabetes Treatment Satisfaction Questionnaire

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).

8.1.4.2 Work Productivity and Activity Impairment General Health questionnaire

The Work Productivity and Activity Impairment General Health (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 year 1 (V3) (and year 2 (V5) for patients in the exploratory phase).

8.1.4.3 Patient Global Impression of Disease Severity and Patient Global Impression of Change

The Patient Global Impression of Disease Severity (PGI-S) is a 1-item measure that assesses the patient's impression of disease severity based on their present diabetes symptoms, i.e., normal, mild, moderate, or severe, whereas the Patient Global Impression of Change (PGI-C) assesses the patient's impression of changes in diabetes symptoms, based on their diabetes symptoms now, compared with how they were before they began taking the randomized treatment i.e., very much better, much better, a little better, no change, a little worse, much worse, very much worse or very severe.

The PGI-S will be administered at the randomization visit (V1.1) and the PGI-C will be administered at year 1 (V3) (and year 2 (V5) for patients in the exploratory phase).

8.1.4.4 Clinician Global Impression of Disease Severity and Clinician Global Impression of Change

The Global Impression of Disease Severity (CGI-S) is a 1-item measure that assesses the clinician's impression of the patient's disease severity, based on the patient's present diabetes symptoms, i.e., normal, mild, moderate, or severe, whereas the Clinician Global Impression of Change (CGI-C) assesses the clinician's impression of change in the patient's diabetes symptoms, based on the patient's diabetes symptoms now, compared with how they were before they began taking the randomized treatment, i.e., normal, mild, moderate, severe or very severe.

The treatment provider will complete the CGI-S at randomization (V1.1) and the CGI-C at the required study visit at year 1 (V3) (and year 2 (V5) for patients in the exploratory phase).

8.1.4.5 Work Limitations Questionnaire

The Work Limitations Questionnaire (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).

8.1.4.6 Dosing conditions

Parameters associated with how oral semaglutide was taken will be collected in a patient questionnaire for the patients randomized to oral semaglutide at year 1 (V3) (and year 2 (V5) for patients in the exploratory phase). This includes amount of fluid taken with the tablet and time from dosing to next meal or drink.

8.2 Safety assessments

This study does not have any safety assessments.

8.3 Adverse events and other safety reporting

The study will employ selected safety collection with focus on all the events listed below:

- 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
- Pregnancies in female patients and pregnancy outcome [until age 1 month] and AEs in the fetus or newborn infant

The definition of AEs, SAEs, medication errors, misuse and abuse can be found in Appendix 3 (Section 10.3).

Some AEs require additional data collection on a specific event form. This always includes medication error, misuse and abuse of randomized treatment. The relevant events are listed in Table 8-1.

Table 8-1 AEs requiring additional data collection (serious and non-serious AEs)

Event type	Additional data collection
Medication error	X
Misuse and abuse	X

The investigator is responsible for detecting, documenting, recording and following up on the AEs listed above. The investigator is responsible for entering safety information into the eCRF within the timelines given Appendix 3 (Section 10.3.5). The investigator is also responsible for contacting

the patient for any required follow-up and follow the event until final outcome, see Appendix 3 (Section 10.3.4).

8.3.1 Time period and frequency for collecting AE information

All AEs and SAEs specified in Section 8.3 (for events related to pregnancy, see Appendix 4, Section 10.4), must be collected from the first study-related activity after the randomization visit and until the end of study visit, at the time points specified in the flowchart including the quarterly chart reviews.

Conditions present prior to the timepoint from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or during other study-related procedures performed before exposure to randomized treatment under clinical investigation, will be recorded as medical history/concomitant illness.

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3.5). All SAEs must be recorded and reported to Novo Nordisk within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek information for AE or SAE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discontinued from/completed the study, and the investigator considers the event to be possibly/probably related to the randomized treatment or related to study participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs

The method of recording, evaluating, and assessing causality of AE and SAE 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.

8.3.3 Follow-up of AEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient. All SAEs should be followed until final outcome of the event or until the patient 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).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study product under clinical investigation 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 product 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 (SUSAR).

8.3.5 Pregnancy

Details of pregnancies in female patients will be collected after first exposure to study product and until the end of study visit. If a female patient becomes pregnant, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

8.3.6 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form. Instructions for reporting technical complaints can be found in Appendix 5 (Section 10.5). 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.

8.4 Baseline assessments

Most baseline assessments to be recorded in this study are to be based on information already available in the patient's medical records. Hence, these data described below is only to be recorded if available and applicable according to local clinical practice.

8.4.1 Treatment provider practice and speciality

At the randomization visit (V1.1) information regarding the treatment provider is to be collected including physician setting and practice and treatment provider specialty (family physician, Endocrinology, Cardiology, Internal medicine or other).

8.4.2 Demography

Demographic data and patient characteristics:

- Year of birth
- Sex (Male/Female)
- Smoking status (Never, Previous, Current)
- Race (White, Black or African American, Asian, Other)
- Ethnicity (Hispanic or Latino or not)
- Insurance status (Commercial, Medicare or Medicaid)

Socio-demographic parameters (reimbursement status, occupational-status, highest level of education, area of residence (classification) are captured by the investigators at the randomization visit (V1.1) and can be captured directly in the eCRF.

8.4.3 Height

Height should be recorded in the eCRF to nearest ¼ inch (inches with two decimals) at randomization (V1.1) only.

8.4.4 Medical and diabetes history

A patient's medical history is a collection of medical events that the patient has experienced in the past. Only relevant medical history, as judged by the treatment provider, should be recorded in the eCRF, including:

- CV risk related medical history

  - atrial fibrillation
  - hypertension
  - dyslipidemia
  - coronary heart disease e.g. myocardial infarction, stable coronary heart disease, unstable angina
  - revascularization e.g. coronary, carotid, peripheral
  - chronic heart failure
  - stroke or transient ischemic attack
  - peripheral artery disease e.g. lower limb arterial disease, carotid, other
  - chronic kidney disease incl. staging
- microvascular complications e.g. diabetic retinopathy neuropathy, nephropathy
- COVID-19

The information collected on medical history should include diagnosis, date of onset and date of resolution or continuation. This, as well as diabetes history, including the date of diagnosis/onset, will be recorded at the randomization visit (V1.1).

It must be possible to verify the patient's medical history in source documents such as the patients' medical record.

9 Statistical considerations

9.1 Statistical hypotheses

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:

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

The power for testing the hypothesis will be calculated.

9.2 Analysis sets

All endpoints will be analyzed based on the Full Analysis Set (FAS). The FAS consist of all randomized patients and patients in the FAS will contribute to the evaluation "as randomized".

9.3 Statistical analyses

9.3.1 Primary endpoint, primary estimand analysis

The primary endpoint will be analyzed using the primary estimand and the first exploratory estimand (see Section 3.3).

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. 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 estimated treatment difference (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. 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.[16]

Superiority for the primary endpoint will be considered established if the upper limit of the 95% confidence interval for the estimated treatment difference is less than 0, or equivalently if the unadjusted two-sided p-value is significant on a 5% level and the estimated treatment difference is in favor of semaglutide for the analyses of the primary estimand.

9.3.2 Primary endpoint, first exploratory estimand analysis

The first exploratory estimand 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. 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 subcutaneous) 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 be the same as that described for the primary estimand.

9.3.3 Secondary endpoints

Details regarding statistical analyses on all supportive secondary endpoints specified in Section 3.2.2 will be specified in the statistical analysis plan (SAP).

9.3.4 Other analyses

Statistical analyses for further endpoints will be described in the SAP. This includes the analyses for the second exploratory estimand.

All endpoints with time frame ending at year 2 will be summarized descriptively.

9.4 Interim analysis

Not applicable.

9.5 Sample size calculations

The sample size will be chosen to show superiority of oral semaglutide versus "one other oral glucose-lowering medication treatment group" on the primary endpoint.
The sample size calculations are done for the primary estimand.

9.5.1 Expected treatment differences

Assumptions on expected treatment differences in the pragmatic study are based on evidence from the PIONEER phase 3a program and clinical practice data from the IBM Explorys database. No efficacy data from pragmatic studies are available for this sample size calculation.

9.5.2 PIONEER phase 3a studies

In PIONEER 2 (NN9924-4223) oral semaglutide 14 mg was compared to the SGLT-2 inhibitor empagliflozin 25 mg in patients on metformin monotherapy. PIONEER 3 (NN9924-4222) compared both 7 mg and 14 mg oral semaglutide to the DPP-4 inhibitor sitagliptin 100 mg in patients on metformin monotherapy or metformin + SU (47% on metformin +SU). The inclusion criterion "HbA_{1c} 7.0-10.5 % (53-91 mmol/mol) (both inclusive)" was specified in the protocols of both studies.

For the treatment policy estimand, the estimated treatment differences are reported in Table 9-1.

Table 9-1 Estimated treatment differences in PIONEER 2 and PIONEER 3 for the treatment policy strategy

Study	Estimated change from baseline in HbA_{1c} (%)				Estimated treatment difference	
	Week	Oral sema 14 mg	Oral sema 7 mg	Comparator	14 mg vs comparator	7 mg vs comparator
PIONEER 2	52	-1.3	NA	-0.9 (empagliflozin)	-0.4	NA
PIONEER 3	52	-1.2	-1.0	-0.7 (sitagliptin)	-0.5	-0.3

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

9.5.3 IBM Explorys database

Clinical practice data from patients initiating an oral glucose-lowering medication on top of metformin monotherapy were included in this analysis of the database. Data were included regardless of switch in anti-diabetic medication or usage of additional other anti-diabetic medications during the follow-up time of two years (see Table 9-2).

Table 9-2 Observed changes from baseline in HbA_{1c} (%) for patients intensifying diabetes treatment on top of metformin monotherapy from IBM Explorys database

Drug class	Observed data on HbA_{1c} (%) Mean (SD)		
	Baseline	N Year 1	Change from baseline at year 1
All OAD	8.43 (1.72)	7,217	-0.97 (1.81)
Sitagliptin	8.23 (1.58)	1,607	-0.69 (1.70)
Empagliflozin	8.22 (1.59)	182	-0.98 (1.64)
SGLT-2i class	8.47 (1.68)	1,164	-0,99 (1.65)

Abbreviations: N Year 1 = Number of patients with both HbA_{1c} (%) baseline data and follow up data at year 1; OAD = Oral anti-diabetic drug.

9.5.4 Usage of treatment options

Based on the limited clinical practice data from the U.S. market it is assumed that half of the patients in the oral semaglutide group will use the 7 mg dose as the maintenance dose during the study and that the other half will use the 14 mg dose. For the comparator group it is assumed that the partial reimbursement by providing an out-of-pocket maximum for the randomized treatment (see Section 6.2) will lead to extended usage of oral anti-diabetic drugs (OAD)s from the SGLT-2i and DPP-4i class. In LIRA-PRIME (NN2211-4232) with full reimbursement and free choice of drugs, drugs from the SGLT-2i class and the DPP-4i class were used to a similar extent in the comparator group. Therefore, it is assumed that half of the patients in the comparator group will use drugs from the DPP-4i class and the other half will use drugs from the SGLT-2i class.

Based on the assumptions on the usage of the different treatment options in both treatment groups and the evidence on treatment effects the following is expected. The estimated change from baseline in the oral semaglutide group at year 1 is expected to be -1.15 %-points (average of -1.3 %-points as observed for 14 mg in PIONEER 2 and -1.0 %-points as observed for 7 mg in PIONEER 3 at year 1). The estimated change from baseline in the comparator group is expected to be -0.85 %-points (average of -1.0 %-points as observed for the SGLT-2i class in IBM Explorys (rounded from -0.99) and -0.7 %-points as observed for sitagliptin in both IBM Explorys (rounded from -0.69) and PIONEER 3 at year 1). Based on this the expected treatment difference for the primary endpoint is derived as -0.3 %-points.

9.5.5 Standard deviation

Assumptions on common standard deviations (SD) for the change from baseline endpoints are based on data from clinical practice, PIONEER 2 and PIONEER 3 (see Table 9-3).

Table 9-3 Standard deviations for change from baseline in HbA_{1c} (%)

Source	Type	Week	N	Standard deviation
IBM Explorys	Observed clinical practice data (all OAD)	52	7,217	1.81
NorthShore	Observed clinical practice data (all OAD)	52	319	1.91
PIONEER 2	Observed in-trial data (common SD)	52	766	1.1
PIONEER 3	Observed in-trial data (common SD)	52	1,728	1.1

Abbreviations: N = number of patients contributing to the standard deviation; OAD = oral anti-diabetic drug; SD = standard deviation.

It is assumed that the observed SD in the pragmatic study will lie in between the SDs in the clinical studies and the values observed in clinical practice. Collectively, the common SD in the sample size calculation is set at 1.9% for the primary endpoint which is assumed to be conservative as it reflects the observed clinical practice data.

9.5.6 Expected frequency and pattern of missing data

The intercurrent events premature randomized treatment discontinuation and intensification of metformin treatment or use of additional glucose-lowering medication are expected to occur to a similar extent as observed in the PIONEER studies. In PIONEER 2 (year 1 data) premature treatment discontinuation occurred in 17.7 % and 11.0 % of the patients for oral semaglutide 14 mg and empagliflozin 25 mg respectively. Additional glucose-lowering medication was used by 7.0 % and 10.5 % for oral semaglutide 14 mg and empagliflozin 25 mg respectively. In PIONEER 3 numbers were comparable with increased usage of additional glucose-lowering medication for oral semaglutide 7 mg (20.4% at year 1.5) and sitagliptin 100 mg (26.3% at year 1.5).

In the setup of the pragmatic study the frequency of missing data (e.g. due to withdrawals by patient) is assumed to be slightly higher than in the PIONEER studies (ca. 7% missing HbA_{1c} (%) data at year 1 for PIONEER 2 and ca. 6-10 % at year 1.5 for PIONEER 3). First data from the semaglutide s.c. pragmatic study (NN9535-4416) on 123 patients showed that 90% of these patients had a HbA_{1c} (%) measurement at year 1.

The missing data will be imputed using a pattern mixture model with multiple imputation and pattern defined by randomized treatment and treatment status at year 1. For the primary estimand the treatment effect will be estimated regardless of the intercurrent events premature randomized treatment discontinuation and intensification of metformin use or use of additional glucose-lowering medication.

9.5.7 Power calculation

The power for the primary endpoint is calculated utilizing two-sample t-test assuming equal variances across treatment groups. The results of the power calculation are shown in Table 9-4.

Table 9-4 Statistical power assuming a sample size of 1,262 patients for the primary endpoint for the primary estimand

Assumption	ETD; SD (Year 1)	Power (Year 1)
Sample size calculation	-0.3; 1.9	80%
SA 1: Lower SD	-0.3; 1.7	87%
SA 2: Higher SD	-0.3; 2.1	71%
SA 3: Lower effect	-0.2; 1.9	46%
SA 4: Higher effect	-0.4; 1.9	96%

Abbreviations: ETD = estimated treatment difference; SA = sensitivity analysis; SD = standard deviation.

As stated above assumptions for the sample size calculations are based on clinical practice data and data from PIONEER phase 3a studies conducted as part of the oral semaglutide development program. Data from the IBM Explorys database and Health Systems provided information on the efficacy and variability in clinical practice. Due to the lack of efficacy data from clinical practice for oral semaglutide, data from the phase 3a studies had to be taken into account as well. It is assumed that these data are the best source of available evidence for the sample size calculation. However, it remains unclear to what extent the assumptions made are applicable to the setup of a pragmatic study.

9.5.8 Summary and conclusion

The final number of patients to be randomized in the study is 1,262 to confirm the hypothesis of superiority for the primary endpoint with a power of 80%.

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 [17] and applicable ICH Good Clinical Practice Guidelines (GCP).[18]
- Applicable laws and regulations.

The protocol, informed consent form, 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, reports on SAEs, and the CSR according to national requirements.

Any amendments 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 patients.

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

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 procedure.
- 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 CTR synopsis to the IRB/IEC.
- reporting any potential serious breaches to the sponsor immediately after discovery.

10.1.2 Financial disclosure

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.

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the patient and/or the patient's legally authorized representative (LAR) and answer any and all questions regarding the

study. This discussion can be done virtually. This includes the use of an impartial witness where required according to local requirements.

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

Patients must be informed that their participation is voluntary. Patients must be informed about their privacy rights. Patients or their LAR will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[18], Declaration of Helsinki[17] 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 authorized 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.

Patients and/or their LAR must be re-consented to the most current version of the informed consent form*(s)* during their participation in the study.

A copy of the informed consent form(s) must be provided to the patient or the patient´s LAR.

The consenting process can be done virtually if all the above elements are incorporated.

10.1.4 Information to patients during the study

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

10.1.5 Data protection

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

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

The patient 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 patient.

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

Personal data may be collected from patients 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.

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.

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will be disclosed according to other applicable requirements, relevant recommendations and regulations, such as the Declaration of Helsinki[17], the International Committee of Medical Journal Editors (ICMJE)[19], the Food and Drug Administration Amendment Act (FDAAA)[20], European Commission Requirements [21, 22] and in accordance with Novo Nordisk commitment to clinical transparency. If a patient 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 patient. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA, see Section 4.4 for definition of PCD.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

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

All patient data relating to the study will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk (e.g. PROs and claims data). The investigator is responsible for verifying that data entries are accurate and correct electronically signing the CRF.

The following will be provided as paper CRFs:

- Pregnancy forms
- Technical complaint forms

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

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 eCRF as soon as possible, preferably within 5 working days after the data becomes available. 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). Direct access includes permission to examine, analyze, verify and reproduce any record(s) and report(s) that are important to the evaluation of the study. If the electronic medical record 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 remote monitoring visits and between remote 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 authorized 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[18], 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 patients are being protected.

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

Monitors will review the patient's medical records and other source data, to ensure consistency and/or identify omissions compared to the eCRF.

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.

10.1.9 Source documents

All data entered in the eCRF must be verifiable in source documentation, other than the CRF i.e. the patient's medical record.

For ePROs, data in the service providers database is considered source data.

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the site.

Data that are transcribed into the eCRF 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 the patients' medical history in source documents, such as patients 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 15 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 must be able to access his/her study documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other patient data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other patient data (in an electronic readable format must be retained by the site. A copy of all data will be stored by Novo Nordisk.

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

10.1.11 Study and site closure

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 patients 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, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of patients by the investigator

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, and well-being of the patients.

A qualified physician, who is an investigator or a sub investigator for the study, must be responsible for all study-related data recording and reporting activities. The treatment provider is responsible for all customary medical treatment 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 study master file. The documents, including the patient identification code list must be kept in a secure locked facility so that no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organizational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorized 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 organizational safety measures have been taken.

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.

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 Rybelsus®. 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 product, 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 disease and/or product 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 lead 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.

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. Novo Nordisk is committed to the development of manuscripts and other publications in an ethical and transparent manner. This includes following guidelines such as International Committee of Medical Journal Editors (ICMJE), Good Publication Practice (GPP-3), and others included in journal or congress “Instructions to Authors.

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. Novo Nordisk establishes an agreement with each author engaged in Novo Nordisk-supported publication activities (including manuscripts, abstracts, posters and slides for oral presentations and publication steering committees) to ensure that all involved parties have a clear understanding of their roles and responsibilities and ethical obligations.

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.[23]

In accordance with ICMJE criteria, anyone involved in the publication including Novo Nordisk employees, who meets all the following four authorship criteria must be named an author:

1. Make a substantial contribution to conception, and design, acquisition of data or analysis and interpretation of data
2. Be involved in the drafting or revision of the publication for important intellectual content
3. Provide approval of the final version to be published
4. Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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. Individuals who do not meet all criteria for authorship but who have made significant contributions to the publication shall be listed upon their documented consent in a section of the publication titled "acknowledgements" or other appropriate sections. This includes Novo Nordisk contributors and/or employees of agencies providing statistical, editorial and medical writing support. The role and specific contributions of each contributor must be described.

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

For a multi-center clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or patients, 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[24], 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.

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in Table 10-1 and Table 10-2 will be performed by the local laboratory used by the treatment provider.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• HbA_{1c} • FPG

Abbreviations: FPG = fasting blood glucose; HbA_{1c} = glycosylated hemoglobin A1c.

Table 10-2 Protocol required safety laboratory assessments

Laboratory assessments	Parameters
Biochemistry and lipids	• Creatinine • Triglycerides • LDL and HDL cholesterol • Total cholesterol
Urinalysis	• UACR

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; UACR = urine albumin to creatinine ratio.

10.3 Appendix 3: Adverse events and serious adverse events: Definitions and procedures for recording, evaluation, follow-up and reporting

10.3.1 Definition of AE

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

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 administration of randomized treatment 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 randomized treatment 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 AE:

- 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 randomized treatment. *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 any untoward medical occurrence 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 patient 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 hospitalization or prolongation of existing hospitalization
    - Hospitalization signifies that the patient 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 hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
    - Hospitalization 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: Hospitalizations 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, diarrhea, 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 hospitalization but may jeopardize the patient 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 randomized treatment
  - 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

An AE requiring additional data collection is an AE where Novo Nordisk has evaluated that additional data is needed in the evaluation of safety.

Medication error:

- A medication error is an unintended failure in the process of providing randomized treatment that leads to, or has the potential to lead to, harm to the patient, such as:
  - administration of wrong drug and/or use of wrong device
    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 patient were likely to happen as judged by the investigator, although they did not necessarily occur.

Note that drug pauses/drug holidays are allowed and is not to be reported as a medication error.

Misuse and abuse:

- Situations where the randomized treatment is intentionally and inappropriately used not in accordance with the protocol (e.g., overdose to maximize effect)
- Persistent or sporadic, intentional excessive use of randomized treatment 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 a 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.

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

10.3.4.1 AE and SAE recording

SAEs and AEs listed in Section 8.3 and AEs/SAEs in connection with pregnancies, must be recorded by the investigator 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 patient identifiers, with the exception of the patient ID, must be redacted on the copies of the source documents before submission to Novo Nordisk.

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 "AE and SAE reporting via paper CRF" later in this section.

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**: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities. 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 randomized treatment and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

Relationship between an AE/SAE and the randomized treatment 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 randomized treatment.

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

The investigator should use the product information for the 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 patient 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 patient 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 patient has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae**: The patient 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 patient has not improved, and the symptoms are unchanged, or the outcome is not known. 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 patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient 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 patient 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.

New or updated information should be recorded in the CRF.

10.3.5 Reporting of SAEs

AE and SAE reporting via CRF

Relevant forms (AE and safety information form) 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):

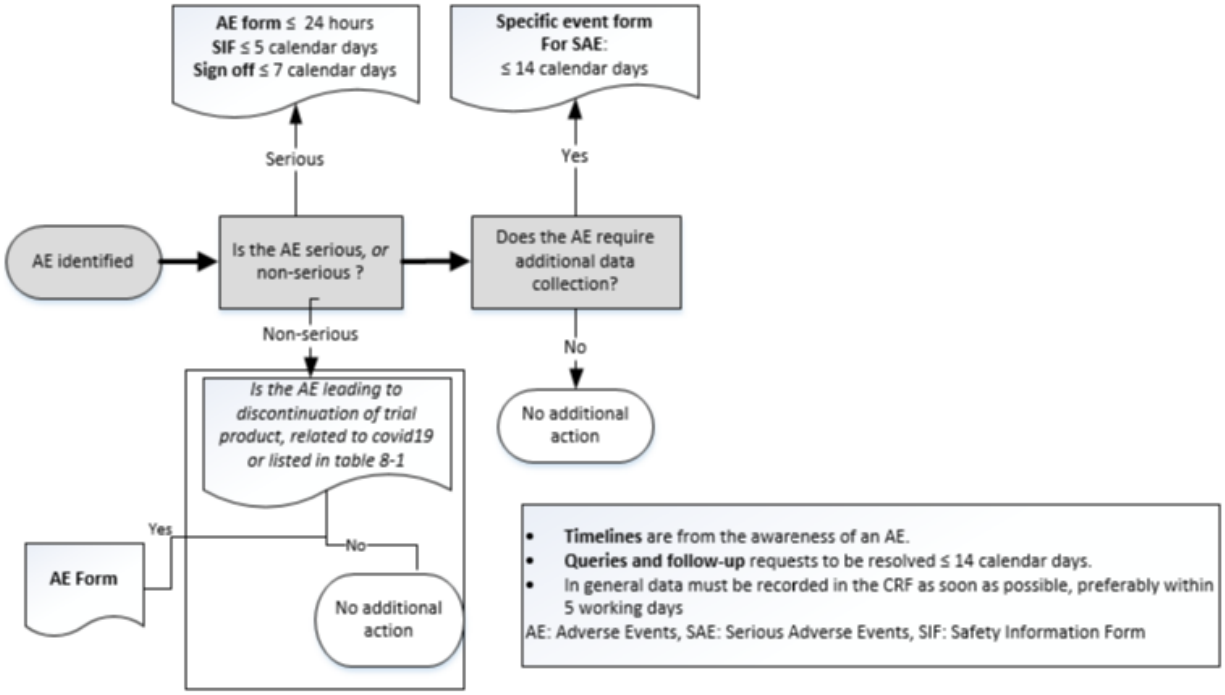
- AE form within 24 hours
- Safety information form within 5 calendar days
- Both forms must be signed within 7 calendar days after first knowledge by the investigator
- Specific event form within 14 calendar days.

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 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 site receives a report of a new SAE from a patient or receives updated information on a previously reported SAE after CRF decommission, the site can report this information on a paper AE and safety information form (see below) or to Novo Nordisk by telephone

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



10.4 Appendix 4: Collection of pregnancy information

Female patients who become pregnant

Investigator will collect pregnancy information on any female patient 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 patient's pregnancy (see Figure 10-2).

Patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on patient 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 fetal status (presence or absence of anomalies) or indication for procedure.

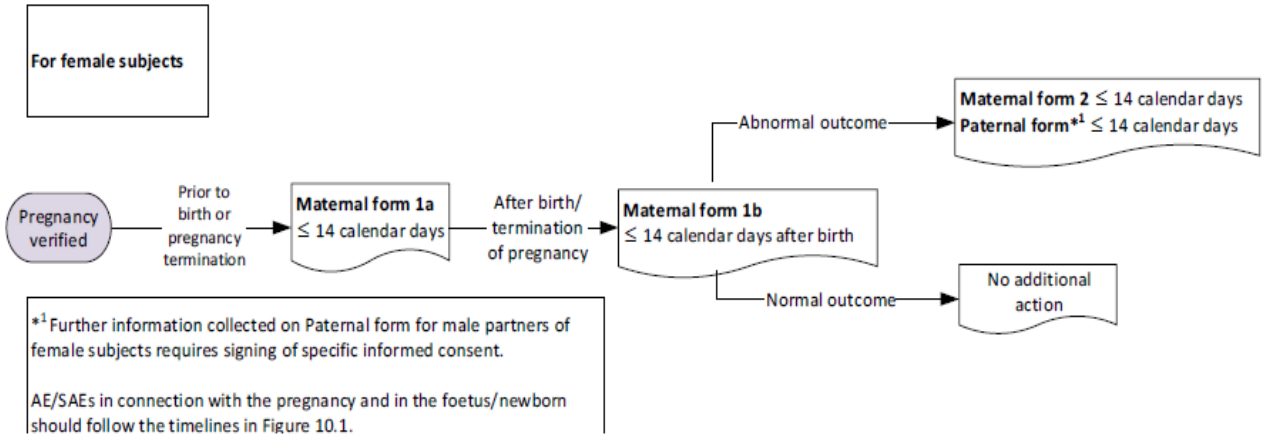
While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding “gestational”, “pregnancy related” or a similar term when reporting the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

Pregnancy outcome should be documented in the patient's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, fetal 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.

Any SAE occurring as a result of a post-study pregnancy which is considered possibly/probably related to the randomized treatment by the investigator will be reported to Novo Nordisk as described in Appendix 3 (Section 10.3.2). While the investigator is not obligated to actively seek this information in former patients, he or she may learn of an SAE through spontaneous reporting.

Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy



Any female patient who becomes pregnant while participating in the study will discontinue Rybelsus® if that is their assigned treatment.

10.5 Appendix 5: Technical complaints: Definition and reporting

Technical complaints on Rybelsus® which occur from the first time of usage of the product until the last time of usage of the product and which is considered related to:

- an adverse event leading to product discontinuation
- an SAE

must be reported to Novo Nordisk via study specific technical complaint form and according to the instructions found in Appendix 5 (Section 10.5.2).

In order for Novo Nordisk to perform a complete investigation of a reported SAE which is not linked to a technical complaint, Novo Nordisk might ask the investigator to complete a technical complaint form for Rybelsus®.

Technical complaints on Rybelsus® NOT related to an adverse event, or related to an adverse event which is not systematically collected according to protocol, may be reported to Novo Nordisk affiliate via the spontaneous reporting system.

Technical complaint on non Novo Nordisk products may be reported to the manufacturing authorization holder of the given product. Still any adverse events or SAEs for the non-Novo Nordisk product must be reported according to Appendix 3 (Section 10.3.2).

10.5.1 Technical complaint definition

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 Rybelsus® (e.g. discoloration, particles or contamination).
- Problems with packaging material including labelling.

10.5.2 Technical complaint reporting

Recording and follow-up of technical compliant to Novo Nordisk

The investigator must complete and forward the technical complaint form to Customer Complaint Center, Novo Nordisk, within:

- 24 hours if related to an SAE.
- 5 calendar days if related to an adverse event leading to product discontinuation.

Contact details for Customer Complaint Center:

- E-mail: CCC-clinicaltrials@novonordisk.com. Note if sending by e-mail: Due to personal data protection, the TC form must be sent as password protected file (WinZip). The password must be provided in a separate e-mail.
- Address: For sending form and samples by courier:
  4010F01 Returvarer
  Customer Complaint Center
  Novo Nordisk A/S, Building 9DS
  Krogshoejvej 55
  Bagsvaerd 2880
  Denmark DK

Follow-up of technical complaints

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

10.5.3 Collection, storage and shipment of technical complaint samples

For technical complaints on Rybelsus®

Technical complaints on Rybelsus® must be reported on the study-specific technical complaint form.

The investigator must collect the technical complaint sample and all associated parts available 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 and a copy of the associated adverse event form(s). 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

corresponding technical complaint form and adverse event form(s) must be kept together for clear identification.

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

Other technical complaints

Instructions will be provided by Novo Nordisk affiliate or the relevant manufacturing authorization holder.

10.6 Appendix 6: Abbreviations

Abbreviation	Definition	Abbreviation	Definition
ADA	American Diabetes Association	HEDIS	Healthcare Effectiveness Data and Information Set
AE	adverse event	ICH-GCP	Good Clinical Practice
ANCOVA	analysis of covariance	ICMJE	International Committee of Medical Journal Editors
CRF	case report form	ID	identifier
CGI-C	Clinical Global Impression of Change	IRB	institutional review board
CGI-S	Clinician Global Impression of Disease Severity	LAR	legal authorized representative
CV	cardiovascular	LPLT	last patient last treatment
DBL	data base lock	LPLV	last patient last visit
DPP-4	dipeptidyl peptidase 4	OADs	oral anti-diabetic drug
DTSQc	Diabetes Treatment Satisfaction Questionnaire, change version	PCD	primary completion date
DTSQs	Diabetes Treatment Satisfaction Questionnaire, status version	PGI-C	Patient Global Impression of Change
EASD	European Association for the Trial of Diabetes	PGI-S	Patient Global Impression of Disease Severity
eCRF	electronic case report form	PRO	patient reported outcome
ER	emergency room	SAE	serious adverse event
eGFR	estimated glomerular filtration rate	SAP	statistical analysis plan
ETD	estimated treatment difference	SD	standard deviation
FAS	full analysis set	SGLT-2	sodium-glucose co-transporter 2
FDA	Food and Drug Administration	T2D	type 2 diabetes mellitus
FPG	fasting plasma glucose	UACR	urine albumin to creatinine ratio
GLP-1 RA	glucagon-like peptide-1 receptor agonists	WLQ	Work Limitations Questionnaire
HbA_{1c}	glycosylated hemoglobin A1c	WPAI-GH	Work Productivity and Activity Impairment, General Health
HCRU	health care resource utilization		

10.7 Appendix 7: Protocol amendment history

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

Overall rationale for preparing protocol, version 4.0:

This amendment is revising inclusion criteria 4 to be more closely aligned with the revised physician insert January 2023. Changes to the content of the protocol are presented in greater detail in the table below. Text in ~~strikethrough~~ has been deleted. *Italicized* text has been inserted.

Section # and name	Description of change	Brief rationale
1.1 Synopsis and 5.1 Inclusion criteria	Revised inclusion criteria #4: Treatment with metformin as monotherapy ~~for a period of at least 90 days~~ prior to eligibility assessment *that has failed to result in adequate glycemic control at the discretion of the investigator or treatment provider*. However, prior short-term treatment with an oral glucose lowering agent or insulin for up to 14 consecutive days in addition to metformin is allowed if discontinued prior to screening.	To more closely align with revised physician's insert.

Overall rationale for preparing protocol, version 3.0:

This amendment is to ensure study completion within business critical timelines with sufficient number of patients for securing adequate power to analyze the primary endpoint. To this end, it has been decided to reduce the study duration for each patient from 2 years to 1 year. By implication, it has been necessary to remove the key secondary endpoint, change in HbA_{1c} from randomization to *year 2* (%-points), as the study is no longer a 2-year study. The primary endpoint, change in HbA_{1c} from randomization to *year 1* (%-points), is preserved. This allows for a reduction in patients screened and randomized from approximately 1,900 screened and 1,688 randomized to approximately 1,388 screened and 1,262 randomized.

Thus, all patients will participate for 1 year. A subgroup of these patients will continue to participate for a second year. This subgroup will consist of patients enrolled prior to protocol version 3.0. All other patients, that is, patients enrolled from protocol version 3.0 and onwards, will participate for 1 year only (see Figure 4-1).

Changes to the content of the protocol are presented in greater detail in the table below.

Section # and name	Description of change	Brief rationale
Title page and 1.1 Synopsis	'Long-term' has been removed from title and text.	To reflect the reduction in study duration.
Throughout	The word physician has been replaced with the word treatment provider in all cases where it is not given that the treatment provider will be a physician.	For accuracy.

Section # and name	Description of change	Brief rationale
Throughout	The phrase 'other glucose-lowering medication' has been changed to '*one* other glucose-lowering medication' in the places where this was not already the case (except the title).	For accuracy and consistency, both within the document and in relation to the SAP.
1.1 Synopsis and 3.2.2 Secondary endpoints	Key secondary endpoint has been deleted.	As it is no longer a 2-year study for all patients.
1.1 Synopsis	Text has been modified to reflect the reduction in study duration.	To ensure study completion within business critical timelines with sufficient number of patients for securing adequate power to analyze the primary endpoint.
1.1 Synopsis	Number of patients have been modified: 1,388 screened instead of 1,900 to achieve 1,262 instead of 1,688 randomized.	To reflect the updated sample size needed for endpoints included.
1.2 Flowchart	The flowchart has been modified to reflect that year 2 is now an exploratory phase with participation only from the subgroup of patients enrolled prior to protocol version 3.0.	To reflect the reduction in study duration with only a subgroup participating in year 2 (the exploratory phase).
1.2 Flowchart	Patients participating in the exploratory phase will now both receive the dosing conditions questionnaire at year 1 and year 2. Previously it was only administered at year 2.	To safeguard against losing data regarding dosing conditions as a consequence of potential drop-outs (see also change description for section 8.1.4.6 Dosing Conditions).
CCI [redacted]		
3.3 Estimands	Estimands have been modified to accommodate for the changes in objectives and endpoints.	For consistency.

Section # and name	Description of change	Brief rationale
4.1 Overall design	The study design (Figure 4-1) has been modified to reflect that year 2 is now an exploratory phase with participation only from the subgroup of patients enrolled prior to protocol version 3.0.	To clearly communicate the differences between the study and the exploratory phase.
8 Study assessments and procedures, 8.1.3.1 HbA_{1c} and FPG, 8.1.3.2 Lipids, creatinine and urinary albumin-to-creatinine ratio, 8.1.4.1 Diabetes Treatment Satisfaction Questionnaire, 8.1.4.2 Work Productivity and Activity Impairment General Health questionnaire, 8.1.4.3 Patient Global Impression of Disease Severity and Patient Global Impression of Change, 8.1.4.4 Clinician Global Impression of Disease Severity and Clinician Global Impression of Change, 8.1.4.5 Work Limitations Questionnaire, 8.1.4.6 Dosing conditions	Text has been added to reflect that patients enrolled from protocol 3.0 coming into effect and onwards will only have assessments done at year 1 whereas patients enrolled prior to protocol 3.0 coming into effect will still have assessments done at both year 1 and year 2.	To clearly communicate the differences between the study and the exploratory phase.
8.1.4 PROs and treatment satisfaction questionnaires	The following text has been added: "If the patient or treatment provider is unable to complete the questionnaire electronically, they will be provided a paper version."	To ensure that patients who are unable to complete questionnaires electronically have another option.
8.1.4.6 Dosing conditions	Patients participating in the exploratory phase will now both receive the dosing conditions questionnaire at year 1 and year 2. Previously it was only administered at year 2.	To safeguard against losing data regarding dosing conditions as a consequence of potential drop-outs (see also change description for section 1.2 Flowchart).
8.1.5 Administrative claims data	Text has been modified to reflect that data can be collected for up to 2 years after the respective patient's study randomization.	To reflect that some patients will be enrolled for up to 2 years.
9 Statistical considerations	Section has been modified to reflect the changes to objectives and endpoints.	For consistency.

Protocol version 2, including version 1: 31 May 2022, global

Overall rationale for preparing protocol, version 2.0:

Changes have been made to inclusion criteria to lower the number of screen-failures in the study without compromising study integrity or subject safety. Furthermore, reimbursement has been changed from partial to full to remove potential impact of out-of-pocket costs between the treatment groups.

Changes to the content of the protocol are presented in the table below.

Based on evaluation by Novo Nordisk and input from an external Expert Panel, the changes introduced will have no impact on efficacy endpoints or subject safety.

Section # and name	**Description of change**	**Brief rationale**
Section 1.1 Synopsis	Deletion of the word *other* which appears twice in the same sentence regarding randomization and oral glucose-lowering medication.	For clarification and improved readability.
Section 1.1 Synopsis	Changes to key inclusion criteria: Treatment with metformin as monotherapy for a period of at least 90 days prior to eligibility assessment has been modified with the following allowance: prior short-term treatment with an oral glucose lowering agent or insulin for up to 14 consecutive days in addition to metformin is allowed if discontinued prior to screening.	To lower the number of screen-failures.
Section 5.1 Inclusion criteria	Changes to key inclusion criteria 4: Treatment with metformin as monotherapy for a period of at least 90 days prior to eligibility assessment has been modified with the following allowance: prior short-term treatment with an oral glucose lowering agent or insulin for up to 14 consecutive days in addition to metformin is allowed if discontinued prior to screening.	To lower the number of screen-failures.
Section 6.2 Co-pay assistance	Reimbursement has been changed from partial to full.	To remove potential impact of out-of-pocket costs between the treatment groups.

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