Cover Page for SAP

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04982575
Sponsor trial ID:	NN9838-4862
Official title of study:	Efficacy and safety of co-administration of cagrilintide s.c. 2.4 mg and semaglutide s.c. 2.4 mg once weekly in subjects with type 2 diabetes
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* Document date refers to the date on which the document was most recently updated.
Note: The date in the header of Page 2 is the date of compilation of the documents and not of an update to content.

16.1.9 Documentation of statistical methods

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Statistical Analysis Plan

Efficacy and safety of co-administration of cagrilintide s.c. 2.4 mg and semaglutide s.c. 2.4 mg once weekly in subjects with type 2 diabetes

Substance name/number: cagrilintide, semaglutide

Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

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Author: [redacted], Biostatistics Obesity and Nash

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Version History

This Statistical Analysis Plan (SAP) for study NN9838-4862 is based on the protocol version 2.0 dated 16 June 2021.

SAP Version	Date	Change	Rationale
1.0	12-Mar-2022	Not Applicable	Original version

1 Introduction

This SAP includes detailed procedures for executing the statistical analyses of the primary and secondary endpoints. Statistical analyses and a number of clarifications additional to those specified in the trial protocol are pre-specified with this SAP. All changes to the statistical analyses planned in the trial protocol are documented in section 2.8.

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

Changes to the analyses described in the protocol are described in 2.8.

1.1 Objectives, Endpoints, and Estimands

1.1.1 Primary objectives

To compare the effect of co-administered semaglutide and cagrilintide versus semaglutide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- change from baseline (week 0) to week 32 in HbA_{1c} (%-point)

1.1.2 Secondary objectives

To compare the effect of co-administered semaglutide and cagrilintide versus semaglutide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- other parameters for glycaemic control
- body weight

To compare the effect of co-administered semaglutide and cagrilintide versus cagrilintide in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- HbA_{1c}
- other parameters for glycaemic control
- body weight

To compare the effect of co-administered semaglutide and cagrilintide, in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor on:

- safety and tolerability
- hypoglycaemia

1.1.3 Estimands

A primary and an additional estimand is defined for the primary objective. Two intercurrent events are identified: treatment discontinuation and initiation of anti-diabetic rescue intervention. The attributes for the estimands are summarised in Table 1-1.

Primary estimand

The primary estimand addresses the main question of interest: What is the effect of co-administered semaglutide and cagrilintide versus semaglutide on change in HbA_{1c} (%-points) from baseline to week 32 in subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor, had all subjects remained on trial treatment without use of rescue medication (anti-

diabetic). A hypothetical strategy is applied for both intercurrent event of premature treatment discontinuation and initiation of rescue medication. The population level summary is difference in means.

The primary estimand estimates the achievable treatment effect without the confounding of treatment discontinuation and initiation of rescue intervention. This approach is considered relevant for evaluating a mechanistic effect.

Additional estimand for the primary objective

The additional estimand addresses a different question of interest: What is the effect of co-administered semaglutide and cagrilintide versus semaglutide on HbA_{1c} (%-points) from baseline to week 32 in subjects with T2D inadequately controlled with metformin with or without SGLT2 inhibitor, regardless of premature treatment discontinuation or initiation of rescue medication (anti-diabetic).

For the additional estimand, the treatment policy strategy is applied for both the intercurrent event of initiation of premature treatment discontinuation and rescue medication. The population-level summary is difference in means. Results based on the additional estimand are expected to mirror the clinical practice for the population scenario because the estimand considers both the efficacy and tolerability of treatments.

Table 1-1 Attributes for the estimands

Estimand category	Treatment condition	Variable/ Endpoint	Population of interest	Intercurrent event strategy	Population-level summary measure
Primary	The effect of co-administered semaglutide and cagrilintide versus semaglutide on HbA_{1c}, both as add-on to metformin with or without SGLT2 inhibitor and without rescue medication	Change in HbA_{1c} (%-point) from baseline to week 32	Subjects with T2D inadequately controlled on metformin with or without SGLT2 inhibitor	Hypothetical strategy for • Initiation of any rescue medication • Treatment discontinuation	Difference in means
Additional	The effect of co-administered semaglutide and cagrilintide versus semaglutide on HbA_{1c}, both as add-on to metformin with or without SGLT2 inhibitor			Treatment policy strategy for • Initiation of any rescue medication • Treatment discontinuation	

1.2 Primary, secondary and exploratory endpoint(s)

1.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline (week 0) to week 32	%-point

1.2.2 Secondary endpoints

1.2.2.1 Confirmatory secondary endpoints

Not applicable for this trial.

1.2.2.2 Supportive secondary endpoints

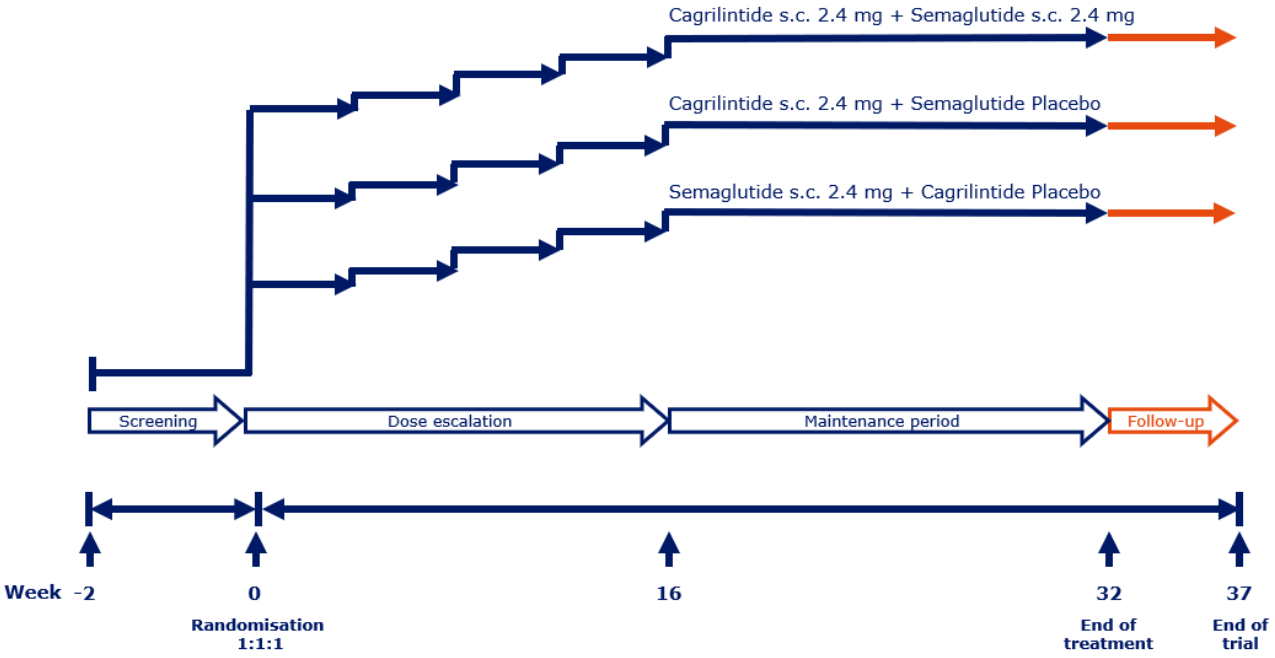
Endpoint title	Time frame	Unit
Efficacy		
Change in fasting plasma glucose (FPG)	From baseline (week 0) to week 32	mmol/L and mg/dL
CGM: Change in mean glucose	From baseline (week 0) to week 32	mmol/L and mg/dL
CGM: Time above range (TAR) >10.0 mmol/L (>180 mg/dL)	At week 32	% of readings
CGM: Time in range (TIR) 3.9–10.0 mmol/L (70–180 mg/dL)	At week 32	% of readings
Change in body weight	From baseline (week 0) to week 32	%
Change in body weight	From baseline (week 0) to week 32	Kg
Safety		
Number of treatment emergent adverse events (TEAEs)	From baseline (week 0) to week 37	Count
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0mmol/L (54mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline (week 0) to week 37	Count of episodes

For the secondary efficacy endpoints change in fasting plasma glucose (FPG), CGM: Change in mean glucose, and change in body weight the primary and additional estimands are modified by substituting the relevant assessment for HbA1c.

1.3 Study Design

Approximately 90 eligible subjects with T2D will be randomised to 1 of the 3 treatment arms in a ratio of 1:1:1. Randomisation will be stratified according to the SGLT2 inhibitor treatment (Yes/No). The trial design is illustrated in Figure 1-1. An interim analysis is planned when last subject has concluded the week 20 visit 12. Further details are found in the study protocol.

Figure 1-1 Schematic diagram of the trial design



2 Statistical considerations

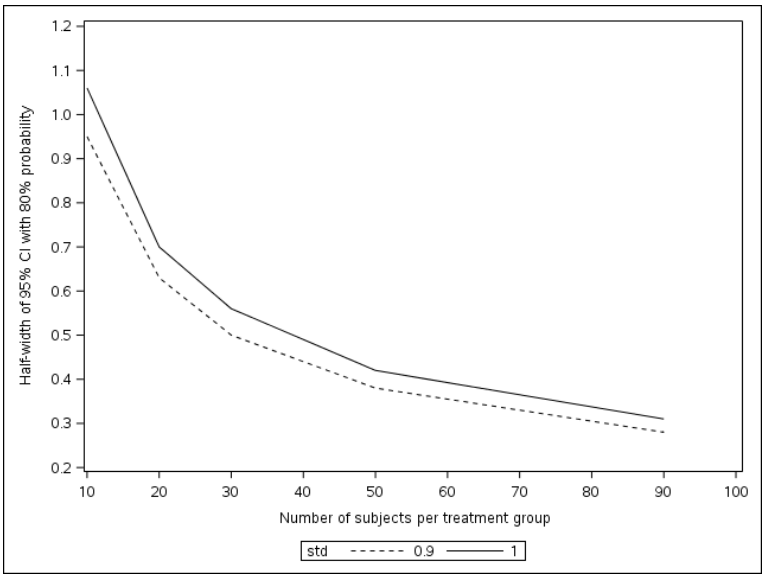
2.1 Statistical hypotheses

No confirmatory statistical hypothesis testing will be done in this trial. Treatment differences will be reported with 2-sided 95% confidence intervals.

2.2 Sample size determination

As the present study is exploratory the sample size calculation is not based on confirmatory testing but aims at quantifying the magnitude of expected variation in the treatment difference for the primary endpoint supporting the primary objective. For the primary estimand a standard deviation of 0.9 (STEP 2) or 1 is assumed for HbA_{1c} change from baseline to week 32. With 30 randomised subjects per treatment arm approximately 80% probability is achieved for obtaining a 95% confidence interval of the treatment difference with half-width 0.5 and 0.56 %-points, respectively. The achievable half-width (with roughly 80% probability) versus sample size is shown in Figure 1-2 for different choices of sample size. Based on this, a sample size of 30 randomised subjects per treatment arm, i.e. a total of 90 randomised subjects, is considered sufficient.

Figure 1-2. Half-width of 95% CI for treatment difference on HbA_{1c} change obtained with 80% power versus sample size by standard deviation (std).



2.3 Populations for analyses

The following population*s* are defined:

Population	Description
Full analysis set (FAS)	All subjects randomised.
Safety analysis set (SAS)	All randomised subjects and who take at least 1 dose of trial product.

The subjects or observations to be excluded from the analysis sets and the reasons for their exclusion must be documented before unblinding and will be described in the CTR. Efficacy endpoints will be analysed using the FAS and safety endpoints will be analysed using the SAS. For both the primary estimand and the additional estimand, subjects contribute to the analysis according to the randomised treatment.

Three observation periods are defined for each subject:

- The in-trial period is defined as the time interval from date of randomisation to date of last contact with trial site.
- The on-treatment period is a subset of the 'in-trial' observation period and represents the time period where subjects are considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following:
    - The date of last dose of trial product +35 days for AEs and hypoglycaemic episodes/ + 14 days for other endpoints
    - The end-date for the 'in-trial' observation period

The on-treatment period will be used for reporting AEs and hypoglycaemic episodes.

The on-treatment without rescue medication period is a subset of the 'on-treatment' observation period and represents the time period where subjects are considered exposed to trial product but

have not initiated any rescue medications. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following:

1) Initiation of rescue medication
2) The last date of the on-treatment period

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

Data points collected outside an observation period will not be included in the analysis. Baseline data will always be included in an observation period.

For the primary estimand, the on-treatment without rescue medication period will be used for reporting of efficacy endpoints. For the additional estimand, data from the in-trial observation period is used.

2.4 Statistical analyses

2.4.1 General considerations

Handling of missing baseline data

The latest available measurement at or prior to randomisation is used as the baseline measurement.

If no measurements have been obtained at or prior to randomisation, the mean value at randomisation across all subjects is used as the baseline value.

2.4.2 Primary endpoint

Analysis addressing the primary estimand

HbA_{1c} (%-point) change from baseline will be analysed using a mixed model for repeated measurements (MMRM). Week 32 assessments for retrieved drop-outs are not used in this analysis. The MMRM will use assessments only from subjects who are taking the randomised treatment until end of treatment or until first discontinuation of randomised treatment defined as 2 consecutive missed doses. The derived date of the second consecutive missed dose will be used as the latest date for using assessments in this MMRM. For subjects who initiate rescue medication before completion or first discontinuation of randomised treatment, the date of starting rescue medication will be used as latest date for using assessments in this MMRM. The MMRM will be fitted using HbA_{1c} change with treatment and stratification factor as factors and baseline HbA_{1c} as covariate – all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed. If this model is not feasible, the model will be simplified by first excluding the stratification factor from the model and, if necessary, using a Toeplitz (second choice) or compound symmetry (third choice) covariance matrix.

The present MMRM model will be used to derive estimates of treatment differences with 95% confidence intervals for cagrilintide 2.4 mg/semaglutide 2.4 mg versus semaglutide 2.4 mg (primary objective) and versus cagrilintide 2.4 mg (secondary objective) together with p-values for the 2-sided tests of no treatment differences.

Analyses addressing the additional estimand

The analysis model for change in HbA_{1c} (%-point) is an ANCOVA with randomised treatment and stratification factor as factors and baseline HbA_{1c} as a covariate. The additional estimand will be based on the FAS using all available week 32 measurements from the in-trial observation period. Missing week 32 data will be imputed from retrieved subjects off treatment by multiple imputation (RDMI) using an ANCOVA model with the same factors and covariate as for the analysis model. If necessary for feasibility, this model will be simplified by successively excluding the stratification factor and treatment factor until convergence is reached. If the reduced RDMI model is infeasible an MMRM model similar to the one used for the primary estimand but including all data regardless of treatment adherence or rescue medication will be used.

The present model will be used to derive estimates of treatment differences with 95% confidence intervals for cagrilintide 2.4 mg/semaglutide 2.4 mg versus semaglutide 2.4 mg and versus cagrilintide 2.4 mg together with p-values for the 2-sided tests of no treatment differences.

2.4.3 Secondary endpoint(s)

2.4.3.1 Confirmatory secondary endpoint(s)

Not applicable for this trial.

2.4.3.2 Supportive secondary endpoints

CGM endpoints 'time in target range' and 'time above target range' will be calculated as 100 times the number of recorded measurements in the given glycaemic range, divided by the total number of recorded measurements. Prior to calculation of CGM endpoints extremely low values will be handled according to below rules.

Extremely low CGM values:

- Values < 14 mg/dL will be set to missing
- Values between 14 and 39 mg/dL will be set to 39

2.4.4 Other safety analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively, including any notable changes of clinical interest in laboratory parameters.

2.4.5 Other analyses

Not applicable for this trial.

2.4.5.1 Pharmacokinetic modelling

Data from the trial may be used for exploratory pharmacokinetic analysis as needed.

2.5 Interim analyses

In order to inform early phase 3 stop/go decision and initiate potential phase 3 planning, interim analyses are planned at week 20 and may include the following endpoints:

- Change from baseline to week 20 in HbA_{1c}
- Change from baseline to week 20 in FPG
- CGM endpoints
  - Mean glucose change from baseline to week 20
  - Time in target range at week 20
  - Time above target range at week 20.
- Change from baseline to week 20 in body weight
- Number of treatment emergent adverse events (TEAEs)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0mmol/L (54mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)

In addition the following parameters may be assessed by descriptive statistics:

- Vital signs
  - Systolic blood pressure
  - Diastolic blood pressure
  - Pulse

Statistical analyses during the interim will be based on the primary estimand. The above lab parameters, vital signs, adverse events and hypoglycaemic episodes are summarised using descriptive statistics.

A minimum number of Novo Nordisk personnel will be unblinded to perform the interim evaluations. After unblinding, these people cannot be involved in daily trial activities until DBL. No change in trial design can occur and the trial will not be stopped for either positive efficacy or futility at the interim evaluations. It is not considered a protocol deviation if an interim analysis is not performed. Further information on the interim evaluations will be specified in an interim charter before unblinding.

2.6 Data monitoring committee

Not applicable for this trial.

2.7 Reporting of the main part of the trial

A DBL is planned shortly after last subject last visit. The trial will be reported after this DBL.

2.8 Changes to Protocol-planned Analyses

- No interim is planned for visit week 32

- The option of using a Toeplitz covariance matrix in the primary MMRM model in case the model can not converge with an unstructured covariance matrix is added.
- The imputation model for RDMI may be further reduced: If necessary for feasibility, this model will be simplified by successively excluding the stratification factor and treatment factor until convergence is reached. If the reduced RDMI model is infeasible an MMRM model similar to the one used for the primary estimand but including all data regardless of treatment adherence or rescue medication will be used.
- A short description of estimands and statistical analyses of secondary efficacy endpoints is added.
- Minor editorial changes are made

3 Supporting Documentation

3.1 Appendix 1: List of abbreviations

AE	*adverse events*
ANCOVA	*analysis of covariance*
CI	*confidence interval*
DBL	*database lock*
FAS	*full analysis set*
MMRM	mixed model for repeated measurements
RDMI	Retrieved drop-outs multiple imputation
SAP	*statistical analysis plan*
SAS	*safety analysis set*
std	*standard deviation*
TEAE	*treatment emergent adverse events*
TFL	*tables, figures and listings*

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Clinical Trial Report

Trial ID: NN9838-4862

MedDRA searches within safety focus areas

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List of abbreviations and definitions of terms

HLT	high level term
MedDRA	Medical Dictionary for Regulatory Activities
NEC	not elsewhere classified
NNMQ	Novo Nordisk MedDRA query
PT	preferred term
SMQ	standardised MedDRA query
SOC	system organ class

1 MedDRA searches for safety focus areas in study NN9838-4862

The MedDRA search strings in this document (ordered alphabetically) were used for the NN9838-4862 clinical trial report. The MedDRA version used was 25.0.

2 Abuse and misuse

Custom query (NNMQ Abuse and Misuse):

- SMQ Drug abuse and dependence (contains only narrow terms)
- HLT Intentional product misuses
- Additional PTs
    - Poisoning deliberate
    - Intentional dose omission
    - Performance enhancing product use
    - Completed suicide
    - Intentional self-injury
    - Suicide attempt
    - Assisted suicide
    - Suspected suicide attempt
    - Suspected suicide.

3 Acute gallbladder disease

Custom query (NNMQ Gallbladder-related disorders) (narrow terms only):

- SMQ Infectious biliary disorders
- SMQ Functional, inflammatory and gallstone related biliary disorders including all sub-SMQs (Biliary tract disorders, Biliary system related investigations, signs and symptoms, Gallbladder related disorders and Gallstone related disorders)

4 Acute renal failure

SMQ Acute renal failure (narrow terms only)

5 Acute pancreatitis

Custom Query (NNMQ Acute pancreatitis):

- SMQ Acute pancreatitis (narrow terms only)
- HLT Acute and chronic pancreatitis (including primary and secondary terms not included in the SMQ Acute pancreatitis)

6 Allergic reactions

Custom Query (NNMQ Allergic reactions) (narrow terms only):

- SMQ Anaphylactic reaction
- SMQ Anaphylactic/anaphylactoid shock conditions
- SMQ Angioedema
- SMQ Hypersensitivity
- SMQ Severe cutaneous adverse reactions

7 Cardiovascular disorders

Custom Query (NNMQ Cardiovascular disorders) (narrow and broad terms):

- SMQ Central nervous system vascular disorders
- SMQ Vasculitis
- SMQ Ischaemic heart disease
- SMQ Cardiac arrhythmias
- SMQ Cardiac failure
- SMQ Cardiomyopathy
- SMQ Embolic and thrombotic events including sub-SMQs: Embolic and thrombotic events, arterial, Embolic and thrombotic events, venous, and Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous
- SMQ Shock including sub-SMQs: Anaphylactic/anaphylactoid shock conditions, Hypoglycaemic and neurogenic shock conditions, Hypovolaemic shock conditions, Shock-associated circulatory or cardiac conditions (excl. torsade de pointes), Torsade de pointes, shock-associated conditions, and Toxic-septic shock conditions
- SMQ Torsade de pointes/QT prolongation

8 COVID-19

SMQ COVID-19 (narrow and broad terms)

9 Gastrointestinal disorders

Custom query (NNMQ Gastrointestinal disorders SOC):

- SOC Gastrointestinal disorders (primary terms only)

10 Hepatic disorders

SMQ Drug related hepatic disorders, comprehensive search (narrow and broad terms)

11 Injection site reaction

Custom Query (NNMQ Injection site reactions):

- HLT Administration site reactions NEC (primary and secondary terms)
- HLT Application and instillation site reactions (primary and secondary terms)
- HLT Infusion site reactions (primary and secondary terms)
- HLT Injection site reactions (primary and secondary terms)

12 Medication error

SMQ Medication errors (narrow and broad terms)

13 Neoplasms

Custom Query (NNMQ Neoplasm):

- SMQ Biliary neoplasms (narrow and broad terms)
- SMQ Breast neoplasms, malignant and unspecified (narrow and broad terms)
- SMQ Liver neoplasms, benign (incl. cysts and polyps)(narrow and broad terms)
- SMQ Liver neoplasms, malignant and unspecified (narrow and broad terms)
- SMQ Malignancies (narrow and broad terms)
- SMQ Malignant lymphomas (narrow and broad terms)
- SMQ Oropharyngeal neoplasms (narrow and broad terms)
- SMQ Ovarian neoplasms, malignant and unspecified (narrow and broad terms)
- SMQ Premalignant disorders (narrow and broad terms)
- SMQ Prostate neoplasms, malignant and unspecified (narrow and broad terms)
- SMQ Skin neoplasms, malignant and unspecified (narrow and broad terms)
- SMQ Uterine and fallopian tube neoplasms, malignant and unspecified (narrow and broad terms)
- SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (primary and secondary terms)

14 Rare events

Custom Query (NNMQ Rare events), excluding PTs from other safety focus areas:

- SMQ Agranulocytosis (narrow terms only)
- SMQ Cholestasis and jaundice of hepatic origin (narrow and broad terms)
- SMQ Guillain-Barre syndrome (narrow terms only)
- SMQ Haematopoietic cytopenias affecting more than one type of blood cell (narrow and broad terms)
- SMQ Haematopoietic leukopenia (narrow and broad terms)
- SMQ Haematopoietic thrombocytopenia (narrow terms only)

- SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow terms only)
- SMQ Hepatitis, non-infectious (narrow and broad terms)
- SMQ Interstitial lung disease (narrow terms only)
- SMQ Neuroleptic malignant syndrome (narrow terms only)
- SMQ Noninfectious myocarditis/pericarditis (narrow terms only)
- SMQ Pseudomembranous colitis (narrow terms only)
- SMQ Retroperitoneal fibrosis (narrow terms only)
- SMQ Severe cutaneous adverse reactions (narrow terms only)
- SOCs: Congenital, familial and genetic disorders (contains only primary terms)
- HLTs: Angioedemas (primary and secondary terms), Glomerulonephritis and nephrotic syndrome (primary and secondary terms), Nephritis NEC (primary and secondary terms).
- PTs: Disseminated intravascular coagulation, Multiple organ dysfunction syndrome and Hepatic lymphocytic infiltration

15 Retinal disorders

Custom Query (NNMQ Retinal disorders):

- SMQ Retinal disorders (narrow terms only)
- HLT Visual impairment and blindness (excluding colour blindness) (primary terms only)

16 Suspected transmission of infectious agent via trial product

Custom Query (NNMQ Transmission):

- HLT Infectious disorders carrier (primary terms only)
- HLT Infectious transmissions (primary terms only)