Cover Page for Statistical Analysis Plan

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Statistical Analysis Plan (SAP)

NN9535-4844 NOVONORDISK

SAFETY AND TOLERABILITY OF WEEKLY SEMAGLUTIDE 0,5 MG OR 1,0 MG IN CHILEAN SUBJECTS WITH TYPE 2 DIABETES
A 6 MONTHS PROSPECTIVE, OPEN-LABEL, NON-CONTROLLED STUDY IN THE CHILEAN PUBLIC HEALTH CARE SYSTEM STUDY

Version 1.0 of 24 February 2022 (Protocol)

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V1.0; 29 Jun 2022 (SAP)

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

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0, 29 Jun 2022 for Protocol NN9535-4844.

The SAP signature page applies to both SAP text and SAP Templates (outputs shells or Table/ Listing/ Figure (TLF) shells). Templates must be sent to the client with the first draft SAP text.

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1. ABBREVIATIONS

ADA	ADA American Diabetes Association
ADE	ADE adverse device effect
AE	AE adverse event
AESI	AESI adverse event of special interest
ALT	ALT alanine aminotransferase
AST	AST aspartate aminotransferase
ATTD	ATTD Advanced Technologies & Treatments for Diabetes
BG	BG blood glucose
CI	Confidence interval
COA	COA clinical outcome assessment
CRF	CRF case report form
CRO	CRO contract research organization
CSR	CSR clinical study report
CTFG	CTFG clinical trial facilitation group
CVOT	CVOT cardiovascular outcome trial
DFU	DFU directions for use
DMC	DMC Data Monitoring Committee
DNA	DNA deoxyribonucleic acid
DPS	DPS data points set
DRE	DRE disease related event
DUN	DUN dispensing unit number
EAC	EAC Event Adjudication Committee
EAS	EAS event adjudication system
ECG	ECG electrocardiogram
eCRF	eCRF electronic case report form
FAS	FAS full analysis set
FDA U.S.	FDA U.S. Food and Drug Administration
FDAAA	FDAAA FDA Amendments Act
FPG	FPG fasting plasma glucose
FSH	FSH follicle-stimulating hormone
GCP	GCP Good Clinical Practice
HbA1c	HbA1c glycated hemoglobin
HIV	HIV Human Immunodeficiency Virus
HRT	HRT hormone replacement therapy
IB	IB investigator's brochure

ICE	ICE intercurrent event
ICH	ICH International Council for Harmonization
IEC	IEC independent ethics committee
IHSG	IHSG The International Hypoglycemia Study Group
IMP	IMP investigational medicinal product
IND	IND investigational new drug
IRB	IRB institutional review board
ISO	ISO International Organization for Harmonization
ISPAD	ISPAD International Society for Pediatric and Adolescent Diabetes
IWRS	IWRS interactive web response system
LAR	LAR legally acceptable representative
LDL	LDL low-density lipoprotein
MDR	MDR Medical Device Regulation
NIMP	NIMP non-investigational medicinal product
PAS	PAS participant analysis set
PCD	PCD primary completion date
PG	PG plasma glucose
PRO	PRO patient reported outcome
PT	Preferred term
RNA	RNA ribonucleic acid
SADE	SADE serious adverse device effect
SAE	SAE serious adverse event
SAF	Safety analysis set
SAP	SAP Statistical Analysis Plan
SMPG	SMPG self-measured plasma glucose
SUSAR	SUSAR suspected unexpected serious adverse reaction
T2D	Type 2 Diabetes
TMM	TMM Trial Materials Manual
USADE	USADE Unanticipated serious adverse device effect
WOCBP	WOCBP woman of childbearing potential

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of demographic and clinical characteristics, safety, tolerability, efficacy and clinical outcomes. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 1.0, dated 24-Feb-2022 and case report forms (CRFs) v1.0, dated 21-Feb-2022.

3. STUDY OBJECTIVES

3.1 Primary Objectives

To evaluate the short-term safety and tolerability (very common and common treatment-emergent adverse events) of once-weekly subcutaneous semaglutide in subjects with type 2 diabetes (T2D), added to available standard of the Chilean public health setting.

3.2 Secondary Objectives

To evaluate the effect on glycaemic control, body weight and other secondary safety and laboratory outcomes associated with once-weekly subcutaneous semaglutide in subjects with T2D added to available standard of care in a Chilean public health care setting (which includes medical, nurse and nutritionist care and available drugs in the public system, metformin, SUs and insulins)

3.3 Primary endpoints

Number of treatment-emergent adverse events from day 1 to week 24 of treatment (Count of subject).

3.4 Secondary endpoints

- Change from baseline in glycosylated hemoglobin (HbA1c) after 24 weeks of treatment (% point).
- Subject achieving HbA1c < 7,0% after 24 weeks of treatment (yes/no).
- Change from baseline of fasting plasma glucose (FPG) after 24 weeks of treatment (mg/dL).
- Change from baseline of body weight after 24 weeks of treatment (kg).
- Change from baseline of waist circumference after 24 weeks of treatment (cm).
- Subjects achieving ≥ 5% and ≥ 10% weight reduction after 24 weeks of treatment (yes/no)
- Change from baseline in laboratory tests after 24 weeks of treatment (Lab test unit correspondent).
- Subject discontinued due to adverse events (treatment discontinuation) from day 1 to week 24 of treatment (yes/no).
- Number of severe hypoglycemic episodes per subject from day 1 to week 24 of treatment (count per subject).
- Number of severe or blood glucose confirmed symptomatic hypoglycemic episodes per subject from day 1 to week 24 of treatment (count per subject).
- Number of serious adverse events (SAEs) per subject from day 1 to week 24 of treatment (count per subject).
- Number of adverse reactions (ARs) per subject from day 1 to week 24 of treatment (count per subject).
- Number of serious adverse reactions (SARs) per subject from day 1 to week 24 of treatment (count per subject).
- Number of suspected unexpected serious adverse reactions (SUSARs) per subject from day 1 to week 24 of treatment (count per subject).
- Change from baseline in heart rate (pulse) after 24 weeks of treatment from day 1 to week 24 of treatment (bpm).
- Treatment duration
- Time to event (since treatment initiation)

[redacted]

4. STUDY DESIGN

4.1 General Description

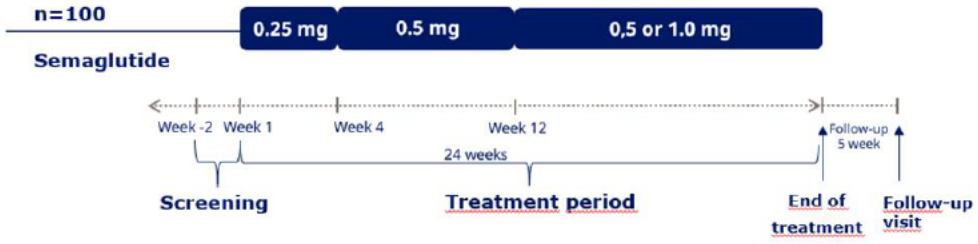
This is an interventional, single-country, multi-center, one-arm, open-label, study.
According to the inclusion and exclusion criteria, investigators will select 100 subjects after screening their local subjects, in each hospital.

The 100 selected subjects will be ≥18 years-old with T2D diagnosed ≥ 90 days prior to the screening visit, in need of treatment optimization with at least 1 antidiabetic drug: metformin, sulphonylureas, meglitinides, DPP-4 inhibitors, SGLT-2 inhibitors, thiazolidinediones, basal or bolus insulin, whose T2D is not well controlled as defined by HbA1C (7.5%-10%). Subjects using GLP-1 RAs will not be permitted in this study. Subject eligibility is based on the subjects' medical history, including HbA1c as part of their routine laboratory tests.
The study will be conducted in the secondary care setting (outpatient), in 3 public hospitals in Chile. The maximum study duration for the individual subjects will be up to 34 weeks, +/- 10 days. The study includes an up to 2-week screening period, followed by a 24-week treatment period and a 5-week follow up period after end of treatment.

The interventions will be providing the study treatment (Ozempic® pens) and laboratory tests required by the protocol, on top of standard of care. GLP-1 RAs are not part of the public hospitals´drug arsenal, which is the reason Novo Nordisk is providing the medication.

Please see **Figure 1** for a schematic overview of the study

[redacted]



4.2 Schedule of Events

The schedule of events can be found in Section 8 of the protocol.

4.3 Changes to Analysis from Protocol

Not applicable.

5. PLANNED ANALYSES

1. Final Analysis

5.1 Final Analysis

All final, planned analyses identified in this SAP will be performed by [redacted] Real World (RW) Biostatistics following Sponsor Authorization of this Statistical Analysis Plan and Database Lock process.

6. ANALYSIS SETS

6.1 All Patients Enrolled Set [ENR]

The all patients enrolled (ENR) set will contain all patients who provide informed consent for this study.

6.2 Full Analysis Set [FAS]

The full analysis set (FAS) will contain all enrolled patients who received at least one dose of study medication.

6.3 In-trial observation period Analysis Set [IAS]

The In-trial observation period analysis set (IAS) will contain all patients in the In-trial Observation period. The observation period is defined as the period from date of initiation to the first date of any of the following, both inclusive:

- Date of end-of-trial follow-up visit
- Date of death
- Date when subject withdrew consent
- Date of last contact for subjects lost to follow-up

6.4 On-treatment observation period Analysis Set [OAS]

The On-trial observation period analysis set (OAS) will contain all Patients in the On-treatment observation period. The observation period is a sub-set of the "in-trial" observation period and represents the period when subjects are considered exposed to the study product.

The observation period starts at the date of first dose of study product and ends at a specific end date according to the flow chart. For adverse events, (excluding hypoglycaemic events), the observation period ends at the first date of any of the following:

- The follow-up visit (P5)
- The premature discontinuation follow-up visit (V4A)
- The last date on the study product + 42 days for safety and +7 days for efficacy
- The end-date for the "in-trial" observation period

7. GENERAL CONSIDERATIONS

7.1 Reference Start Date

Reference start date is defined as the day of the first dose of study medication (Week 1) and will appear in every listing where an assessment date or event date appears.

7.2 Baseline

Baseline is defined as the measurement taken closest to the day of the first dose of study medication (Week 1).

7.3 Windowing Conventions

The maximum study duration for the individual subjects will be up to 34 weeks, +/- 10 days. The study includes an up to 2-week screening period, followed by a 24-week treatment period and a 5-week follow up period after end of treatment.

The following table describes assignment of visit windows to the following data for purposes of analysis:

Table A: Windows conventions

Assigned Study Week (Inclusive)		Visit Assigned
From	**To**	
-2	1 (+/- 10 days)	Visit 1
1	4 (+/- 10 days)	Phone visit 2
4	12 (+/- 10 days)	Visit 3
12	24 (+/- 10 days)	Visit 4
24	29 (+/- 10 days)	Phone visit 5

7.4 Common Calculations

Treatment-emergent Adverse Events (TEAEs) will be reported in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R) for on-treatment period.

All AEs and hypoglycemic episodes will be summarized in terms of number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the incidence rate (number of events per person time) for on-treatment period and ´in-trial´ observation period.

The secondary efficacy endpoints and assessments at scheduled timepoints will be summarized descriptively based on FAS using the on-treatment observation period and the in-trial observation period. Descriptive statistics (mean, Standard Deviation (SD), median, and range for continuous variables and proportion for categorical variables) will be used.

For secondary endpoints (quantitative measurements), change from baseline will be calculated as:
Test Value at Visit X – Baseline Value

The following continuous secondary endpoints will be analyzed statistically based on FAS and the on-treatment observation period:

- HbA1c (%-point)
- Fasting plasma glucose (mg/dL)
- Body weight (Kg, %)
- Waist circumference (cm)
- Fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) (mg/dL)

For continuous secondary endpoints, a mixed model for repeated measurements (MMRM) will use all assessments in the specific observation period. The dependent variable (response) is the change from baseline in HbA1c at all scheduled visits. This model will include time (visits) as fixed factor and HbA1c as covariate. Interactions between visit and baseline HbA1c will also be included in the model. An unstructured covariance matrix will used to describe the variability for the repeated measurements for a patient (if the model will not converge a compound symmetry covariance matrix will be considered as the simpler alternative). Patients without post-baseline measurements for HbA1c will not be included in the analysis. Least-square means estimates for change from baseline in HbA1c at week 24 for an average patient in FAS (i.e. a reference patient with a mean baseline HbA1c) will be reported and include associated 95% CI and p-value that tests the null-

hypothesis of no change from baseline at week 24. The MMRM is a well-established method that appropriately accounts for the uncertainty pertaining to missing data. This analysis assumes that missing data are missing at random (i.e., missing values may be dependent on observed, but not unobserved data).

Fasting blood lipid endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

7.5 Software Version

All analyses will be conducted using Python version 3.6.9. The statistical software used will be reported at the final clinical study report.

8. STATISTICAL CONSIDERATIONS

8.1 Statistical Bias Reduction

The main bias in the mixed model for repeated measurements (MMRM) is the missing data in the depend variable. Therefore, patient without post-baseline measurements for HbA1c will not be included in the analysis. These statistical methods are for the purpose of description, not statistical inference.

8.2 Statistical Tests and Confidence Intervals

Unless otherwise specified in the description of the analyses, a two-sided 95% confidence interval will be considered as a default (alpha= 5%).

8.3 Adjustments for Covariates and Factors to be Included in Analyses

For continuous secondary endpoints, a mixed model for repeated measurements (MMRM) will use all assessments in the specific observation period. The dependent variable (response) is change from baseline in HbA1c at all scheduled visits. This model will include time (visits) as fixed factor and HbA1c as covariate. Interactions between visit and baseline HbA1c will also be included in the model.

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

Primary endpoints:

- Adverse events

Secondary endpoints:

- Adverse events
- Time since treatment initiation to adverse events
- Time since diagnosis to adverse events
- HbA1c (%)
- Fasting plasma glucose (mg/dL)
- Body weight (Kg, %)
- Waist circumference (cm)
- Fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) (mg/dL)

8.4 Missing data

The number of missing data will be reported for each variable of interest in the analysis. For descriptive analysis, missing data will be described separately, and no data imputation will be used. In the MMR analysis and safety analysis missing baseline data will not be imputed.

These statistical methods are for the purpose of description, not statistical inference.

8.5 Examination of Subgroups

Subgroup analyses will be conducted to address potential confounders and effect modifiers associated with the treatment. It should be noted that the study was not designed to detect treatment differences within subgroups.

The following subgroups will be assessed and described within the exploratory analysis sections:

- Gender:
  - Female
  - Male

- Age (years):
  - <30
  - ≥30 to <60
  - ≥60
- Diabetes medications at screening:
  - Metformin
  - Sulphonylureas
  - Meglitinides
  - DPP-4 inhibitors
  - SGLT-2 inhibitors
  - Thiazolidinediones
  - Basal or bolus insulin
- Race
  - Indigenous
  - Black
  - No specific ethnicity
  - Other
  - Unknown
- Site:
  - Site 1
  - Site 2
  - Site 3
- Dose:
  - Dose 1 (0.5 mg at the end of treatment)
  - Dose 2 (1.0 mg at the end of treatment)

8.6 Randomization Schedule

No randomization will be performed for this study

9. OUTPUT PRESENTATIONS

The conventions for presentation of data in outputs is appended to this SAP.

10. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition, withdrawals, and protocol violations, including inclusion and exclusion criteria will be presented for all enrolled subjects.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the FAS. No statistical testing will be carried out for demographic or other baseline characteristics. Only descriptive data will be reported (frequency, mean ± standard deviation, median, interquartile range, minimum and maximum).

The following demographic, medical history and other baseline characteristics will be reported for this study:

Demographic characteristics:

- Age at study screening (in years) - calculated relative to date of consent
- Gender
- Ethnicity

Medical History:

- Complications of diabetes
- High blood pressure diagnosis
- Cardiovascular diseases history
- Thrombotic disease history
- Biliary pathology history
- Tobacco use
- Diabetes medications at screening

Baseline parameters:

- Weight (kg)
- Height (cm)

- Body mass index (BMI) (kg/ m^2)
- Waist circumference (cm)
- Glycosylated hemoglobin (HbA1c)
- Fasting plasma glucose (FPG)
- Fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)

11.1 Derivations

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

12. SURGICAL AND MEDICAL HISTORY

Surgical and Medical History information will be presented for the SAF and FAS.

- Surgical History will be coded using MedDRA coding, version 24.
- Data captured on the Surgical History page of the CRF will be presented by SOC (System Organ Class) and PT (Preferred Term).
- Medical History will be coded using MedDRA coding, version 24.
    - Medical History conditions are defined as those conditions which stop prior to or at Screening.
    - Presented by SOC (System Organ Class) and PT (Preferred Term).

Include details if disease-specific history has been collected.

13. CONCOMITANT ILLNESSES

Concomitant Illnesses are conditions which started prior to Screening and are ongoing at the date of Screening. Concomitant Illnesses will be presented for the SAF and FAS and coded using MedDRA coding, version 24. Concomitant illnesses will be presented by SOC (System Organ Class) and PT (Preferred Term).

14. MEDICATIONS

Medications will be presented for the SAF and FAS and coded using MedDRA coding, version 24.

Specify if preferred Anatomical Therapeutic Chemical (ATC) class coding is performed (check coding guidelines), and if so, under which ATC class medications is summarized (ATC Level 3 should be

considered the default).

If preferred ATC class coding will not be done, specify by which dictionary term(s) the medications will be summarized.

15. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for the SAF. The date of first study medication administration will be taken from the eCRF Therapeutic treatment dose form (form 15). The date of last study medication will be taken from the eCRF Discontinuation of the intervention form (form 22) and End of study form (form 24).

15.1 Derivations

Duration of exposure days = date of last study medication administration – date of first study medication administration + 1.

16. EFFECTIVENESS OUTCOMES

16.1 Primary Effectiveness

The effectiveness outcomes include the effect on glycemic control, body weight, waist circumference and laboratory tests.

16.1.1 Primary Effectiveness Variable(s) & Derivation(s)

The primary effectiveness variables are:

Change in glycosylated hemoglobin (HbA1c) (%) from baseline to 24 week:

Include: form 10 of eCRF

Proportion of subject achieving HbA1c < 7,0% from baseline to 24 week:

Include: form 10 of eCRF

Change of fasting plasma glucose from baseline to 24 week:

Include: form 10 of eCRF

Change of body weight from baseline to 24 week:

Include: form 8 of eCRF

Change of waist circumference from baseline to 24 week:

Include: form 8 of eCRF

Proportion of subjects achieving ≥ 5% and ≥ 10% weight reduction from baseline to 24 week:

Include: form 8 of eCRF

Change in fasting blood lipids from baseline to 24 week:

Include: form 11 of eCRF

16.1.2 Primary Analysis of Primary Effectiveness Variable(s)

The effectiveness outcomes include the effect on glycemic control, body weight, waist circumference and laboratory tests. The primary effectiveness analysis will be performed for the FAS.

For effectiveness outcomes (secondary outcomes), a mixed model for repeated measurements (MMRM) will use all assessments in the specific observation period. The dependent variable (response) is change from baseline in HbA1c at all scheduled visits. This model will include time (visits) as fixed factor and HbA1c as covariate. Interactions between visit and baseline HbA1c will also be included in the model.

Change in glycosylated hemoglobin (HbA1c) (%) from baseline to 24 week:

These endpoints will be analyzed by the MMRM

Change of fasting plasma glucose from baseline to 24 week:

These endpoints will be analyzed by the MMRM

Change of body weight from baseline to 24 week:

These endpoints will be analyzed by the MMRM

Change of waist circumference from baseline to 24 week:

16.1.3 Sensitivity Analysis of Primary Effectiveness Variable(s)

No sensitivity analysis is included in this SAP.

Check that sensitivity analyses are labelled as in the protocol – they are sometimes called secondary analyses of the primary variable, in which case consider putting them in the secondary analysis section to be consistent with the protocol.

Analysis of the primary variable at a different time point should be included in the secondary analysis section.

Include sensitivity analyses if they are mentioned in the protocol.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set (SAF).

17.1 Adverse Events

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 24.

Treatment Emergent Adverse Events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication and prior to the last date of study medication.

Update definition of treatment emergent AEs according to protocol. Also note that some clients are not using the concept of treatment emergent – check with client in advance and alter sections below if appropriate.

If other subsets of AEs are required, e.g. AEs leading to discontinuation from the study, copy section 18.1.2 and modify, ensuring that it is clearly stated how these events are determined from the (e)CRF.

An overall summary of number of subjects (%) within each of the categories described in the sub-section below, will be provided as specified in the templates.

17.1.1 All TEAEs

Incidence of TEAEs and non-Serious AEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication.

17.1.1.1 Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity is classified as severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity is used in the corresponding severity summaries.

17.1.1.2 Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as "not related", "possibly related", "probably related" (increasing severity of relationship). A "related" TEAE is defined as a TEAE with a relationship to study medication as "possibly related" or "probably related" to study medication. TEAEs with a missing relationship to study medication are regarded as "probably related" to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication is used in the corresponding relationship summaries.

17.1.2 TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the discontinuation of the intervention form (form 22).

For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

17.1.3 Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF (form 18). A summary of serious TEAEs by SOC and PT will be prepared.

17.1.4 Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the (e)CRF (form 18). A summary of TEAEs leading to death by SOC and PT will be prepared.

17.2 Deaths

If any subjects die during the study discontinuation of the intervention form (form 22) and end of study form (form 24), the information will be presented in a summary table and a data listing.

17.3 Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for glucose metabolism tests, lipid profile, liver function profile, kidney function profile and quantitative serum human chorionic gonadotropin. A list of laboratory assessments to be included in the outputs is included in Appendix 2 of Protocol NN 9535-4844 version 1.0. Presentations will use SI Units.

17.3.1 Laboratory Specific Derivations

- Estimated glomerular filtration rate (eGFR):

  eGFR=175 x Serum Creatinine Result – 1.154 x age-0.203 x 1.212 (if patient is black) x 0.742 (if female)

  Serum creatinine result: form 13 item 2.1

  Age: form 4 item 2

  Black: form 4 item 4

  Female: form 4 item 3

17.3.2 Laboratory Reference Ranges and Markedly Abnormal Criteria

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

17.4 Vital Signs

The following Vital Signs measurements will be reported for this study:

- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Sitting Pulse Rate (bpm)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Incidence of markedly abnormal values
- Shift from baseline according to markedly abnormal criteria
- Listing of Patients meeting markedly abnormal criteria

17.4.1 Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria.

Variable	Unit	Low	High
Systolic Blood Pressure: SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
Diastolic Blood Pressure: DBP	mmHg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Heart rate	Bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm

17.5 Physical Examination

The following summaries will be provided for physical examination data:

- Incidence of abnormalities at enrollment/ baseline
- Incidence of abnormalities post baseline

18. DATA NOT SUMMARIZED OR PRESENTED

Not applicable.

19. REFERENCES

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EMA. (n.d.). Guideline on Missing Data in Confirmatory Clinical Trials. Retrieved December 15, 2011, from European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf

Little, R., & Yau, L. (1996). Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. Biometrics , vol 52, 1324-1333.

Robins, J. M. & Finkelstein, D. M (2000). Correcting for Noncompliance and Dependent Censoring in an AIDS Clinical Trial with Inverse Probability of Censoring Weighted (IPCW) Log-Rank Tests. Biometrics, vol 56, 779-788.

19.1 APPENDIX 1. Programming Conventions for Outputs

Dates & Times

Depending on data available, dates and times will take the form dd-mmm-yyyy. Partial date is allowed for some entries.

Spelling Format

English US

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

Site ID

Subject ID

19.2 APPENDIX 2. Partial Date Conventions

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study medication (med) start date, then not TEAE If start date >= study medication start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:

START DATE	STOP DATE	ACTION
		If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior/ Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

19.3 APPENDIX 3. Missing data guidance

General considerations

The number of [missing, non-missing] cases will be reported for each variable of interest in the analysis. The flow of study participants through the entire study period will be characterized in terms of the number of subjects who [completed the study, attended each visit, had a claim in each study period, had a physician visit in each study period, withdrew (with reasons described) or died].

Repeated Measures

With repeated measures, the following techniques are recommended as well. Use one but not both unless you have some compelling reason to do otherwise.

19.4 APPENDIX 4. General Style Guidelines

This appendix provides general writing style guidelines. It should be followed as much as possible to make all SAPs consistence. This is an abbreviated version of the AMA Manual of Style, 10th Edition, v.2; for more details, refer to the original document.

ABBREVIATIONS

Use abbreviations if presented 2 or more times; do not abbreviate if only used once in the text

Define abbreviations at first occurrence and follow immediately with the abbreviation in parentheses

Define abbreviations in the Synopsis, again in the main text, and in a footnote each time for all tables/ figures

Definitions are shown in lower case unless it contains a proper noun, is a formal name, or begins a sentence where only the first word of the definition is capitalized

At first mention, names of states, territories, possessions, provinces, or countries should be spelled out when following the name of a city; and spelled out in full when they stand alone within the text

Use 2-letter abbreviations for US and Canadian province names in addresses (with zip code and Canadian postal codes) and in reference lists, tables, and figures, but do not use in the main text

Do not begin sentences with abbreviations or use periods with abbreviations

Do not define units of measure, include on Abbreviations List, or show in plural form

Do not use abbreviations in report titles and avoid using in headings/ subheadings

Do not use punctuation for abbreviations (e.g., etc., i.e., et al, MD, PhD) (Exception: use periods after a person's initials [Hal C. Smith] and also for the abbreviation for number [No.])

CAPITALIZATION

Capitalize the first word and the first letter of each major word in titles/ headings

Capitalize 2-letter verbs in titles (e.g., Is, Be, Go, Do, Am); Note: The word "to" is not capitalized.

Do not capitalize articles, coordinating conjunctions, or a preposition of 3 or fewer letters unless it starts a sentence/ title/ header

Do not capitalize the second part of a hyphenated compound in titles/ subtitles/ text headings; however, if both words in a temporary compound carry equal weight, both would be capped (e.g., Cost-Benefit Analysis, Low-Level Bacteria, B-Cell Lymphoma, Age-Related Macular Degeneration)

Capitalize the first word of a formal statement or a direct quote that follows a colon

Capitalize any geographic names, holidays, languages, nationalities, ethnicities, political parties, religions/ denominations; do not capitalize names of seasons, or "white" or "black" as a designation of race

Do not capitalize the common noun that follows a proper noun in eponyms (e.g., Rose-Waaler test, Down syndrome, Trendelenburg position)

The AMA states not to capitalize any designators except for "Table and Figure" (see pages 378-379 of the AMA); however, it's common practice at Q to capitalize designators and identifiers when used with a number (e.g., Phase, Day, Week, Month, Patient, Patient, Visit, Group, Method, Grade, Section)

DATES AND TIME

The AMA says to use the conventional form for time and dates (e.g., 11:30 PM on February 25, 1961); however, it's common practice at Q to use the "dd Month yyyy" format for all dates (e.g., 05 May 2005); the month should always be spelled out unless listed in a table; do not use a comma when only the month and year are given (e.g., A report was issued May 2005.)

Use standard time (12-hr clock) when referring to the time of day showing AM and PM in small capital letters without any punctuation (e.g., 1:00 AM, 3:00 PM); for clarity, 12:00 midnight or 12:00 noon should be used versus AM or PM

Always spell out "second, minute, hour, day, week, month, and year" in text; ok to abbreviate in tables/

figures/ virgules

GENERAL

Use ", i.e., or , e.g.," with a preceding and following comma without any periods when used within the text; however, parenthetical text only requires the use of a following comma (e.g., XXX)

Always spell out "approximately" versus use of symbol (~) within the text

Use trademark symbol on first reference using the complete name of the product; shown on same line as product name and no superscript

Do not use contractions in regulatory documents

Do not italicize or underline foreign words that have become part of standard English language (e.g., in vivo, in vitro, post hoc, ad libitum, et al.)

Always use "compared with" not "compared to" in regulatory documents (applies to any form of "compare")

HYPHENS

Do not hyphenate numerical ranges shown in text except for ranges expressing fiscal years, academic years, life spans, or study spans or for ranges expressed within parentheses Hyphenate 2-word, 1-thought phrases before nouns (i.e., modifiers), but not when it follows a noun or serves as a predicate adjective (e.g., A treatment-related AE occurred [use hyphen] vs. The AE was treatment related [no hyphen])

Use a hyphen when an unhyphenated word would have an incorrect or confusing meaning (e.g., re-sign [to

sign again] versus resign [as to surrender])

Do not hyphenate adverbs ending in "ly"

The following common prefixes are not joined with a hyphen except when they precede a proper noun,

a capitalized word, or an abbreviation: ante, anti, bi, co, contra, counter, de, extra, infra, inter, intra, micro, mid, neo, non, over, pre, post, pro, pseudo, re, semi, sub, super, supra, trans, tri, ultra, un, and under; however, use a hyphen after a prefix or before a suffix to avoid an awkward combination of letters.

IN-TEXT FIGURES

Figure titles are located above the figure and should include "Figure," Arabic number, meaningful title, and no ending punctuation

Use "title case" for capitalizing the title (i.e., cap the first letter of each major word; cap all prepositions in a title that contain at least 4 letters)

Figures should be consecutively numbered according to the order in which they are mentioned in the text

IN-TEXT TABLES

Table titles are located above the table and should include "Table," Arabic number, meaningful title, and no ending punctuation

Use "title case" for capitalizing the title (i.e., cap the first letter of each major word; cap all prepositions in a title that contain at least 4 letters)

Tables should be consecutively numbered according to the order in which they are mentioned in the text

Column headers should use the title case format set in boldface type; if relevant, the unit of measure should be indicated in the column heading (unless it's given in the row heading)

Table stubs (row headings) are left-justified, shown in sentence case, and indentions are typically used to depict hierarchical components of the stubs

Tables spanning more than one page should have the table number, title, and column headers carried over to each subsequent page of the table; include "continued" after the table title on subsequent pages

Missing data or blank cells within a table should be avoided; use a zero (0) to indicate the value of the data in the cell is zero, an ellipsis (...) may be used, or "N/A" may be included to indicate "not applicable"; however, N/A needs to be defined in an abbreviations footnote

IN-TEXT FIGURE AND TABLE FOOTNOTES

Footnotes is only shown at the bottom of the last page of tables and directly beneath figures

Footnote placement order is as follows: 1) Abbreviations: XXX (shown in alpha order), 2) Footnotes (lower case superscript letters), 3) Statistics (asterisks are only used for statistical footnotes), 4) Source:

Use lowercase, superscript, alphabetic characters for items other than statistical significance; always use a period at the end of each line of footnote text, even if it's not a complete sentence

Place footnotes flush left beneath the table in alphabetical order

Use a font size no larger than the font size used in table; if table font size is reduced, also reduce footnote font

Correct format to use for the abbreviations footnote is as follows: Abbreviations: BP, blood pressure; ND, not determined; SD, standard deviation. (Note: The AMA format is presented; however, an equal symbol with spaces instead of a comma has also been used in Q documents [e.g., BP = blood pressure)

LISTS: BULLETED AND NUMBERED

(Note: The AMA doesn't provide much info on the formatting of lists, so the following text is what's typically used for most documents.)

Lists should be prefaced with an introductory phrase ending in a colon or period

Items in the list should use parallel grammatical form; avoid mixing clauses and full sentences

Do not use ending punctuation if each list item is a fragment

List items shown in full sentences should start with a capital letter and have ending punctuation

NUMBERS

Arabic numerals should be used to express numbers in most circumstances

Use Roman numerals for cancer stages and Arabic numerals for cancer grades

Spell out numbers that begin a sentence, title, subtitle, or heading; accepted usage and numbers used as pronouns; other uses of "one" in running text; numbers spelled out in quotations or published titles

Write common fractions in full (exception: mixed fractions typically use numerals [e.g., 3¼, 2½, no spaces])

Ordinal numbers should be spelled out for first through ninth, but shown as 10th, 11th, etc.; no superscript

Values less than 1, insert a zero before the decimal point (e.g., 0.001 not .001)

Do not hyphenate ranges used in text, use either "to" (i.e., should be used when the final digit isn't included in the span) or "through" (i.e., use when final digit is included in the span); okay to hyphenate ranges used in a table

When spelling out numbers, hyphenate twenty-one through ninety-nine

Do not use a comma when writing a 4-digit number; use a "thin space" for values of 10 000 or more

Use a percent symbol (%) after every percentage, even if it's a zero or used in a series

Use the word "percentage" if no digit/ number has been used

Use a capitalized "P" shown in italics (e.g., P value) when expressing statistical significance using only 2 digits whether or not P is significant; include spaces around the mathematical symbol; do not include a preceding zero before the decimal point (e.g., P = .63 not P = 0.63)

(Note: The format noted above specifically follows the AMA style and is different than what's commonly been used in most Q documents [i.e., a lower case "p" in regular font, without any spaces around the mathematical symbol, and the inclusion of a preceding zero before the decimal point,

p<0.05]); whatever format is chosen needs to be used consistently throughout the entire document

Use either "C" or "F" when reporting temperatures; include after each temperature in a range (37.5°C to 39.6°C) and without any spaces between the number and degree symbol

The AMA says a "thin space" should be used before and after mathematical symbols; however, it's common practice at Q to use no spaces between numbers and symbols (e.g., >5, <4, ±0.54) and spaces around equations and/or ranges (e.g., a = b, 3.0 ± 0.88); use a consistent format throughout the document

Do not repeat a unit with every value in a series or range (e.g., 2, 20, and 40 mL)

Never split digits and units of measure or dates between lines; always use a nonbreaking space command

PREFERRED SPELLING AND FORMAT

Always use consistent format and terminology throughout the document (i.e., if a chosen format is different from the standard AMA format; consistently use either the US English or UK English format, but do not use both unless a term is a proper noun that needs to retain the original spelling, such as International Council for Harmonisation [i.e., retain the "s" and don't change to "z" in Harmonisation, since it's a proper name])

Retain the UK English spelling for MedDRA Preferred Terms within tables, but use US English spelling for the Preferred Terms when shown within the text

PUNCTUATION

When 3 or more items are listed in a series, place a comma before the "and, or" preceding the last item when using US English

Use 1 space after a comma, and 1 or 2 spaces after a colon and/or period; the spacing format chosen for colons and periods should be consistently used throughout the entire document

Use double quotation marks to indicate words or phrases; place commas and periods inside quotation

marks; place colons and semicolons outside quotation marks for US English; use reverse for UK English

Use brackets within parentheses when a parenthetical expression is used within another parenthetical expression- -Exception: reverse the order in mathematical and chemical expressions

Use semicolons when a coordinating conjunction is omitted between 2 complete thoughts

When a semicolon is linked by a conjunctive adverb (e.g., however), a comma must follow the adverb

Use semicolons to separate a series of phrases that already contain commas

REFERENCES

In-Text Citations:

In-text citations should be cited in consecutive numerical order using superscript Arabic numerals; show superscript numbers outside periods and commas, and inside colons and semicolons

Use commas without spaces to separate other parts of a multiple citation (Note: The AMA says when 2 or more references are cited together, use hyphens to join the first and last numbers of a closed series; however, this could potentially cause issues when linking references back to the Reference List when published, so it might be best to separate all numbers with commas/ no spaces and not use a "series format with a hyphen.")

Reference List and Style:

References on the Reference List should be numbered consecutively with Arabic numerals in the order in which they were cited in the text

Preferred method is to include all authors' names within the reference unless there are more than 6, in which case the names of the first 3 authors are used followed by "et al." (Note: The NLM guidelines do not limit the number of authors listed, but for space considerations, AMA decided to depart from the NLM guidelines on this point.)

Example of typical format for a journal reference: McDougle CJ, Stigler KA, Posey DJ. Treatment of aggression in children and adolescents with autism and conduct disorder. J Clin Psychiatry. 2003;64(suppl 4):16-25. (Note: Use no periods after author's initials, include a period after "et al." if it's included, use only 1 space after periods, italicize the journal title abbreviation and end with a period, and use no spaces between the year, volume, issue, and all-inclusive pagination.)

See the AMA Manual of Style, 10th Ed., Chapter 3 for correct formats to use when presenting other types of publications

19.5 TLF Shells

Tables:

Table 1: Patient Disposition
(All Enrolled Patients)

	Total (N=xxx)
Enrolled patients, n	xx
Eligible patients, n (%) [1]	xx (xx.x%)
	xx (xx.x%)
…	xx (xx.x%)
Analysis Set N, n (%) [2]	xx (xx.x%)
Completed study, n (%) [2]	xx (xx.x%)
Discontinued study, n (%) [2]	xx (xx.x%)
Reason for discontinuation [3]	
<Reason 1>, n (%)	xx (xx.x%)
<Reason 2>, n (%)	xx (xx.x%)
…	xx (xx.x%)
<Reason N>, n (%)	xx (xx.x%)

[1] Percentages calculated based on the number of Enrolled patients.
[2] Percentages calculated based on the number of Eligible patients.
[3] Percentages calculated based on the number of patients who discontinued the study.
Percentages are calculated using non-missing values as denominator.

[redacted]

Table 2: Protocol Deviations
(All Enrolled Patients)

	Total (N=xxx) n (%)
Patients with any protocol deviation	xx (xx.x%)
Protocol deviation category 1	xx (xx.x%)
Protocol deviation coded term 1	xx (xx.x%)
Protocol deviation coded term 2	xx (xx.x%)
…	xx (xx.x%)
Protocol deviation coded term N	xx (xx.x%)
Protocol deviation category 2	xx (xx.x%)
Protocol deviation coded term 1	xx (xx.x%)
Protocol deviation coded term 2	xx (xx.x%)
…	xx (xx.x%)
Protocol deviation coded term N	xx (xx.x%)
….	
Protocol deviation category N	xx (xx.x%)
Protocol deviation coded term 1	xx (xx.x%)
Protocol deviation coded term 2	xx (xx.x%)
…	xx (xx.x%)
Protocol deviation coded term N	xx (xx.x%)

[redacted]

[redacted]

	Total (N=xxx) n (%)
Patients with any major protocol deviation	xx (xx.x%)
Protocol deviation category 1	*xx (xx.x%)*
Protocol deviation coded term 1	*xx (xx.x%)*
Protocol deviation coded term 2	*xx (xx.x%)*
…	*xx (xx.x%)*
Protocol deviation coded term N	*xx (xx.x%)*
Protocol deviation category 2	*xx (xx.x%)*
Protocol deviation coded term 1	*xx (xx.x%)*
Protocol deviation coded term 2	*xx (xx.x%)*
…	*xx (xx.x%)*
Protocol deviation coded term N	*xx (xx.x%)*
….	
Protocol deviation category N	*xx (xx.x%)*
Protocol deviation coded term 1	*xx (xx.x%)*
Protocol deviation coded term 2	*xx (xx.x%)*
…	*xx (xx.x%)*
Protocol deviation coded term N	*xx (xx.x%)*

Percentages are calculated using non-missing values as denominator.

[redacted]

[redacted]

Table 3: Demographic Characteristics
(Full Analysis Set)

	Total (N=xxx)
Age at Baseline (years) [1]	
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
Age at Baseline (categories), n (%)	

[redacted]

[redacted]

	Total (N=xxx)
n	xx
< 30	xx (xx.x%)
≥30 to <60	xx (xx.x%)
≥60	xx (xx.x%)
...	
Missing	xx
Gender, n (%)	
n	xx
Male	xx (xx.x%)
Female	xx (xx.x%)
Missing	xx
Ethnicity, n (%)	
n	xx

[redacted]

[redacted]

	Total (N=xxx)
Indigenous	xx (xx.x%)
Black	xx (xx.x%)
No specific ethnicity	xx (xx.x%)
Not Reported	xx (xx.x%)
Other	xx (xx.x%)
Missing	xx
Complications of diabetes, n (%)	
n	xx
Nerve damage (neuropathy) in limbs	xx (xx.x%)
In men erectile dysfunction	xx (xx.x%)
Kidney disease	xx (xx.x%)
Skin conditions	xx (xx.x%)
Eye damage (cataracts, glaucoma, etc.)	xx (xx.x%)
Other	xx (xx.x%)

[redacted]

[redacted]

	Total (N=xxx)
High blood pressure diagnosis	
n	xx
Yes	xx (xx.x%)
No	xx (xx.x%)
Cardiovascular diseases history	
n	xx
Yes	xx (xx.x%)
No	xx (xx.x%)
Thrombotic disease history	
n	xx
Yes	xx (xx.x%)
No	xx (xx.x%)

[redacted]

[redacted]

	Total (N=xxx)
Biliary pathology history	
n	xx
Yes	xx (xx.x%)
No	xx (xx.x%)
Tobacco use	
n	xx
Current smoker	xx (xx.x%)
Former smoker	xx (xx.x%)
Never smoker	xx (xx.x%)
Unknown	xx (xx.x%)
Diabetes medications at screening	
n	xx
Metformin	xx (xx.x%)

[redacted]

[redacted]

	Total (N=xxx)
Sulphonylureas	xx (xx.x%)
Meglitinides	xx (xx.x%)
DPP-4 inhibitors	xx (xx.x%)
SGLT-2 inhibitors	xx (xx.x%)
Thiazolidinediones	xx (xx.x%)
Basal or bolus insulin	xx (xx.x%)

SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum.
Percentages are calculated using non-missing values as denominator.
[1] Age at baseline (years) = (date of baseline visit – date of Birth + 1) / 365.25.

[redacted]

[redacted]

Table 4: Medical History
(Full Analysis Set)

	Total (N=xxx)
Complications of diabetes, n (%)	
n	xx
Nerve damage (neuropathy) in limbs	xx (xx.x%)
In men erectile dysfunction	xx (xx.x%)
Kidney disease	xx (xx.x%)
Skin conditions	xx (xx.x%)
Eye damage (cataracts, glaucoma, etc.)	xx (xx.x%)
Other	xx (xx.x%)
High blood pressure diagnosis	
n	xx
Yes	xx (xx.x%)

[redacted]

[redacted]

	Total (N=xxx)
No	xx (xx.x%)
Cardiovascular diseases history	
n	xx
Yes	xx (xx.x%)
No	xx (xx.x%)
Thrombotic disease history	
n	xx
Yes	xx (xx.x%)
No	xx (xx.x%)
Biliary pathology history	
n	xx
Yes	xx (xx.x%)
No	xx (xx.x%)

[redacted]

[redacted]

	Total (N=xxx)
Tobacco use	
n	xx
Current smoker	xx (xx.x%)
Former smoker	xx (xx.x%)
Never smoker	xx (xx.x%)
Unknown	xx (xx.x%)
Diabetes medications at screening	
n	xx
Metformin	xx (xx.x%)
Sulphonylureas	xx (xx.x%)
Meglitinides	xx (xx.x%)
DPP-4 inhibitors	xx (xx.x%)
SGLT-2 inhibitors	xx (xx.x%)

[redacted]

	Total (N=xxx)
Thiazolidinediones	xx (xx.x%)
Basal or bolus insulin	xx (xx.x%)

SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum.
Percentages are calculated using non-missing values as denominator.

Table 5: Baseline parameters
(Full Analysis Set)

	Total (N=xxx)
Weight (kg)	
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Q1; Q3	xx.x; xx.x

[redacted]

	Total (N=xxx)
Min; Max	xx.x; xx.x
Missing	xx
Height (cm)	
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	
Missing	xx
Body mass index (BMI) (kg/ m2)	
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x

[redacted]

[redacted]

	Total (N=xxx)
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
Waist circumference (cm)	
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
Glycosylated hemoglobin (HbA1c)	
n	xx
Mean (SD)	xx.x (xx.xx)

[redacted]

[redacted]

	Total (N=xxx)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
Fasting plasma glucose (FPG)	
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
Total cholesterol (mg/dL)	
n	xx

[redacted]

[redacted]

	Total (N=xxx)
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
LDL cholesterol (mg/dL)	
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
HDL cholesterol (mg/dL)	

[redacted]

[redacted]

	Total (N=xxx)
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
Triglycerides (mg/dL)	
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx

SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum.
Percentages are calculated using non-missing values as denominator.

[redacted]

[redacted]

Table 6XX: Baseline Vital Signs
(Full Analysis Set)

	Total (N=xxx)	
	Result	Change
Sitting Systolic Blood Pressure (mmHg)		
n	xx	
Mean (SD)	xx.x (xx.x)	
Median	xx.x	
Q1; Q3	xx.x; xx.x	
Min; Max	xx.x; xx.x	
Missing	xx	
…….		
Sitting Diastolic Blood Pressure (mmHg)		
n	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Q1; Q3	xx.x; xx.x	xx.x; xx.x
Min; Max	xx.x; xx.x	xx.x; xx.x
Missing	xx	xx

[redacted]

[redacted]

	Total (N=xxx)	
	Result	Change
Pulse Rate (bpm)		
n	xx	
Mean (SD)	xx.x (xx.x)	
Median	xx.x	
Q1; Q3	xx.x; xx.x	
Min; Max	xx.x; xx.x	
Missing	xx	
…..		

SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum;

[redacted]

[redacted]

Table 6 **Baseline Vital Signs**
(Full Analysis Set)

	Total (N=xxx)
	Result
Sitting Systolic Blood Pressure (mmHg)	
n	xx
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
Sitting Diastolic Blood Pressure (mmHg)	
n	xx
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
Pulse Rate (bpm)	
n	xx
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx

SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum;

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Table 7 – Concomitant Medications
(Full analysis set)

Medication Class (ATC 1)/ Standardized Medical Term	**Total (N=xxx) Number (%) of patients**
Number of patients with any medical medication	xx (xx.x)
<<Medication Class 1>>	xx (xx.x)
<<Standardized Medical Term 1>>	xx (xx.x)
<<Standardized Medical Term 2>>	xx (xx.x)
…	…
<<Standardized Medical Term n>>	xx (xx.x)
…	…
…	…

[redacted]

[redacted]

<<Medication Class n>>	xx (xx.x%)
<<Standardized Medical Term 1>>	xx (xx.x%)
<<Standardized Medical Term 2>>	xx (xx.x%)
...	...
<<Standardized Medical Term n>>	xx (xx.x%)

Medications are coded using the World Health Organization Drug Dictionary (WHO-DD, version WHO-DD **MMMYYYY X** Format).
Patients are counted once per medication class and per standardized medical term.
Number (%) of patients are sorted alphabetically by ATC 1. A patient can have one or more Standardized Medical Terms reported under a given Medication Class.
ATCs are sorted in order of descending frequency for the overall category.
ATC: Anatomic Therapeutic Class – Level 1.

WHO-DD: World Health Organization Drug Dictionary.

Notes:

- Population for concomitant medications should be defined in the statistical analysis plan and might be different from 'full analysis set'.
- Columns in grey might be needed when multiple cohorts, groups or treatments are compared. In this case update headers accordingly.
- Check with data management or medical coding team which WHO-DD version was used and update first footnote accordingly.
- When prior medications, non-drug therapies or surgical/ other procedures are collected and they need to be reported separately use this table format for 'Prior Medications', 'Non-Drug Therapies', 'Surgical/ Other Procedures' and update table's title, label to first column, footnotes and dictionary of standard terms accordingly.

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Table 10: Medical History (full)
(Full Analysis Set)

System organ class/ Preferred term	Total (N=xxx) Number (%) of patients
Number of patients with any medical history	xx (xx.x%)
<<System organ class 1>>	xx (xx.x%)
<<Preferred term 1>>	xx (xx.x%)
<<Preferred term 2>>	xx (xx.x%)
...	...
<<Preferred term n>>	xx (xx.x%)
...	...
...	...

[redacted]

[redacted]

<<System organ class n>>	xx (xx.x%)
<<Preferred term 1>>	xx (xx.x%)
<<Preferred term 2>>	xx (xx.x%)
...	...
<<Preferred term n>>	xx (xx.x%)

MedDRA Version 24.0.
Number (%) of patients are sorted alphabetically by SOC. A patient can have one or more PTs reported under a given SOC.
PT are sorted in order of descending frequency for the overall category.
MedDRA: Medical Dictionary for Regulatory Activities.
SOC: System Organ Class; PT: Preferred Term.
Percentages are calculated using the non-missing as the denominator.

Notes:

- Population for medical history should be defined in the statistical analysis plan and might be different from 'full analysis set'.
- Columns in grey might be needed when multiple cohorts, groups or treatments are compared. In this case update headers accordingly.
- Check with data management or medical coding team which MedDRA version was used and update first footnote accordingly.
- When surgeries are collected and they need to be reported separately use this table format for 'Surgery history' and update table's title accordingly.

[redacted]

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Table 11: Adverse Events by System Organ Class and Preferred Term
(Safety Analysis Set)

	Total (N=xxx)	
System organ class/ Preferred term	Number (%) of patients	Number of events
Any Adverse event	xx (xx.x%)	xx
<<System organ class 1>>	xx (xx.x%)	xx
<<Preferred term 1>>		
<<Preferred term 2>>	xx (xx.x%)	xx
...	xx (xx.x%)	xx
<<Preferred term n>>	xx (xx.x%)	xx
	...	...

[redacted]

[redacted]

...	xx (xx.x%)	xx
...		
	...	...
<<System organ class n>>	...	...
<<Preferred term 1>>		
<<Preferred term 2>>	xx (xx.x%)	xx
...	xx (xx.x%)	xx
<<Preferred term n>>	xx (xx.x%)	xx

MedDRA: Medical Dictionary for Regulatory Activities; SOC: System Organ Class.
PT: Preferred Term.
MedDRA dictionary *version 24.0.*

Notes:

- Number (%) of patients are sorted alphabetically by SOC. A patient can have one or more PTs reported under a given SOC.
- PTs are sorted in order of descending frequency for the overall category.
- Percentages are calculated using the non-missing values as denominator.

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Table 12: Clinical Laboratory Variables Over Time
(Full Analysis Set)

Laboratory variable	SI unit	Group	Time point	Result						Change from Baseline					
				n	Mean (SD)	Median	Q1: Q3	Min: Max	Missing	n	Mean (SD)	Median	Q1: Q3	Min: Max	Missing
Glycosylated hemoglobin (HbA1c)	(%)	<Overall>	Baseline	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						
			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
Fasting plasma glucose (FPG)	mg/dL	<Overall>	Baseline	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						
			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx

[redacted]

			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
Body weight	*Kg*	*<Overall>*	***Baseline***	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						
			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
Waist circumference	*cm*	*<Overall>*	***Baseline***	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						
			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
Total cholesterol	*mg/dL*	*<Overall>*	***Baseline***	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						
			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx

[redacted]

			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
LDL cholesterol	*mg/dL*	*<Overall>*	*Baseline*	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						
			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
HDL cholesterol	*mg/dL*	*<Overall>*	*Baseline*	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						
			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
Triglycerides	*mg/dL*	*<Overall>*	*Baseline*	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						
			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx

[redacted]

[redacted]

			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
SI: The International System of Units; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum.															

[redacted]

Table 13: Vital Signs Variables Over Time
(Full Analysis Set)

Laboratory variable	SI unit	Group	Time point	Result						Change from Baseline					
				n	Mean (SD)	Median	Q1: Q3	Min: Max	Missing	n	Mean (SD)	Median	Q1: Q3	Min: Max	Missing
Sitting Systolic Blood Pressure (mmHg)	mmHg	<Overall>	Baseline	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						
			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
Sitting Diastolic Blood Pressure (mmHg)	mmHg	<Overall>	Baseline	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						

[redacted]

			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
Pulse rate (bpm)	*Kg*	*<Overall>*	*Baseline*	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx						
			Visit 3	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
			Visit 4	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx	xx	xx.x (xx.xx)	xx.x	xx.x: xx.x	xx.x: xx.x	xx
SI: The International System of Units; SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum.															

[redacted]

[redacted]

Table 14: Summary of Treatment Exposure
(Full Analysis Set)

	Total (N=xxx)
Treatment Duration (weeks)[1]	
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
Treatment Dose (mg)	
n	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x

[redacted]

[redacted]

	Total (N=xxx)
Q1; Q3	xx.x; xx.x
Min; Max	xx.x; xx.x
Missing	xx
Dose frequency	
QD	xx (xx.x)
BID	xx (xx.x)
TID	xx (xx.x)
.	xx (xx.x)
.	xx (xx.x)
.	xx (xx.x)
Number of Patients with:	
Treatment interruption	xx (xx.x)
Treatment discontinuation	xx (xx.x)

SD: Standard Deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum;
[1]. Duration (days) = sum of all individual durations defined as (end date of Treatment - start date of Treatment) +1.
QD: Daily, BID: Twice a day, TID: Three times a day.

[redacted]

Table 15: Model Mixed Repeated Measurement for Gycosylated Hemoglobin (HbA1c)

(Full Analysis Set)

Predictor	Categories	Estimate	Standard Error	95%LL	95%UL	p-value
<<Timepoint>>	<Visit 1>	XX.XX	XX.XX			
	(Ref)					
	< Visit 2>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
	< Visit 3>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
<<Predictor 1>>	<Cat 1>	XX.XX	XX.XX			
	(Ref)					
	<Cat 2>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
	<Cat 3>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
<<Predictor 2>>[1]	<Value>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX

[redacted]

Predictor	Categories	Estimate	Standard Error	95%LL	95%UL	p-value

LL: Lower 95% Confidence Limits of the coefficient; UL: Upper 95% Confidence Limits of the coefficient.
[1] <Predictor 2> is a continuous variable; the coefficient represents the estimated effect of a one unit increase in < Predictor 2>.

Notes:

- Predictor 2 is an example of continuous variable. The coefficient indicates the estimated effect of a one unit change in Predictor 2. Adapt the footnote [a] to give the exact name of <Predictor 2>.

[redacted]

[redacted]

Table 16 **Model Mixed Repeated Measurement Model Output for Fasting Plasma Glucose**
(Full Analysis Set)

Predictor	Categories	Estimate	Standard Error	95%LL	95%UL	p-value
<<Timepoint>>	<Visit 1> (Ref)	XX.XX	XX.XX			
	< Visit 2>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
	< Visit 3>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
<<Predictor 1>>	<Cat 1> (Ref)	XX.XX	XX.XX			
	<Cat 2>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
	<Cat 3>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
<<Predictor 2>>[1]	<Value>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX

LL: Lower 95% Confidence Limits of the coefficient; UL: Upper 95% Confidence Limits of the coefficient.

[1] <Predictor 2> is a continuous variable; the coefficient represents the estimated effect of a one unit increase in < Predictor 2>.

Notes:

Predictor 2 is an example of continuous variable. The coefficient indicates the estimated effect of a one unit change in Predictor 2.

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Table 17 **Model Mixed Repeated Measurement Model Output for Body weight**
(Full Analysis Set)

Predictor	Categories	Estimate	Standard Error	95%LL	95%UL	p-value
<<Timepoint>>	<Visit 1> (Ref)	XX.XX	XX.XX			
	< Visit 2>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
	< Visit 3>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
<<Predictor 1>>	<Cat 1> (Ref)	XX.XX	XX.XX			
	<Cat 2>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
	<Cat 3>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX
<<Predictor 2>>[1]	<Value>	XX.XX	XX.XX	XX.XX	XX.XX	0.XXX

LL: Lower 95% Confidence Limits of the coefficient; UL: Upper 95% Confidence Limits of the coefficient.

[1] <Predictor 2> is a continuous variable; the coefficient represents the estimated effect of a one unit increase in < Predictor 2>.

Notes:

Predictor 2 is an example of continuous variable. The coefficient indicates the estimated effect of a one unit change in Predictor 2.

[redacted]