Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02730377
Sponsor trial ID:	NN2211-4232
Official title of study:	LIRA-PRIME: Efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes inadequately controlled with metformin monotherapy and treated in a primary care setting
Document date:	14 January 2020

16.1.9 Documentation of statistical methods

List of contents

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

.

Statistical Programming Specification

Trial ID: NN2211-4232

LIRA-PRIME: Efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes inadequately controlled with metformin monotherapy and treated in a primary care setting

Authors:

[redacted]

Table of contents

Table of Figures

Table of Tables

1 Introduction

1.1 Purpose

This Statistical Programming Specification (SPS) describes decisions for programming and output generation for the trial.

Like the ADRG, the SPS also provides context for the analysis datasets and terminology that benefit from additional explanation beyond the data definition document, define.xml.

Documents referred to in this trial are:

PSPS: nn2211-phase3b-4-project-statistical-programming-specification version 1.0, novoDOCS object ID [redacted]

Table shells: version 1.0 located on P:\nn2211\nn2211-4232\current\stats\document\0300_programming\0310_statistical_programming_specification, and archived in novoDOCS. A list of novoDOCS object IDs can be found in Appendix A

The specifications for the programming of this trial are described in the NN2211-PSPS (see above). Any deviations from and additions to the specifications in the PSPS are described in this document.

1.2 Acronyms

Table 1 Acronyms

Acronym	Translation
ADaM	Analysis Data Model
ADRG	Analysis Data Reviewers Guide
AE	Adverse event
ALCOA (C)	Attributable, Legible, Contemporaneous, Original, Accurate, Complete
BDS	Basic Data Structure
BMI	Body Mass Index
CRF	Case report form
CTR	Clinical trial report
DDD	Defined daily dose
DPP-4	Dipeptidyl peptidase 4
FAS	Full Analysis Set
FPG	Fasting plasma glucose
HbA_{1c}	glycosylated haemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Metadata Management Application

NN	Novo Nordisk
OAD	Oral Antidiabetic Drug
PD	Protocol deviation
PSPS	Project Statistical Programming Specification
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SGLT-2	Sodium/glucose cotransporter 2
SPS	Statistical Programming Specification
TEAE	Treatment emergent adverse event
WHO	World Health Organization

1.3 Study data standards and dictionary inventory

Table 2 gives an overview of versions used for data definitions and documentation.

Table 2 Versions of standards and dictionaries used

Standard or Dictionary	***Versions Used***
SDTM	*SDTM v1.3/SDTM IG v3.1.3*
ADaM	*ADaM Model Document 2.1* *ADaM Implementation Guide v1.1* *ADAM Basic Data Structure for Time-to-Event Analysis v1.0* *ADaM Structure for Occurrence Data (OCCDS) v1.0* *ADaM Supplement to the TAUG-Diabetes v1.0*
Controlled Terminology	*ADaM 2014-09-26*
Data Definitions	*Define.xml version 2.0*
Platform	*HP-UX HP IPF B.11.31 U ia64*
Software	*SAS v9.4 (TS1M2)*

Standard or Dictionary	***Versions Used***
Date of reference (Software specific)	*1 January 1960*
MedDRA	*22.0*
WHO	*WHODrug Global/B3 1 Mar 2019*

1.4 Source data used for analysis dataset creation

The SDTM datasets of the trial are to be used as source data.

1.5 Trial folder structure and naming standards

1.5.1 Naming standard

1.5.1.1 Naming of instances

Electronic record (ER) instances will be used for the CTR instance (at the time of report review Committee (RRC)) and for any output delivered to authorities.

Table 3 Naming of instances

Instance	Name
DBL, RM	Zzz,yyymmdd Where zzz = {dbl, rm,..}
CTR	ctr_yyyymmdd_er

1.5.1.2 Output programs and outputs

Output programs and output names should not contain capital letters or spaces and should follow the following naming standard to the extent possible:

[t|l|f|a|s]_[domain]_[subset]_[sub-subset]_[population].sas

Where t, l, f, a, and s denote tables, listings, figures, analyses and sensitivity analyses, respectively.

1.5.1.3 ADaM programs

The naming of ADaM programs (hereafter referred to as mk-files) should follow the following naming standard:

mk_ssss_adxxxxen.sas

Where (1) is a number so that the mk-files are sorted in the order of execution in UNIX SCE, (2) is a name 2-6 characters long that corresponds to the domain that the data originates from and (3) is a suffix of "en" if the dataset contains endpoints. If (1) is the same for two or more programs, it is assumed that these can be executed in parallel.

1.5.1.4 Macros

Macro names should not contain capital letters or spaces. The names should include "adam" as prefix if they are used in the production of ADaM data.

2 Protocol description

2.1 Protocol number and title

This SPS is applicable to the NN2211-4232 trial, 'LIRA-PRIME: Efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes inadequately controlled with metformin monotherapy and treated in a primary care setting', protocol version 2.0 dated 01-JUN-2016.

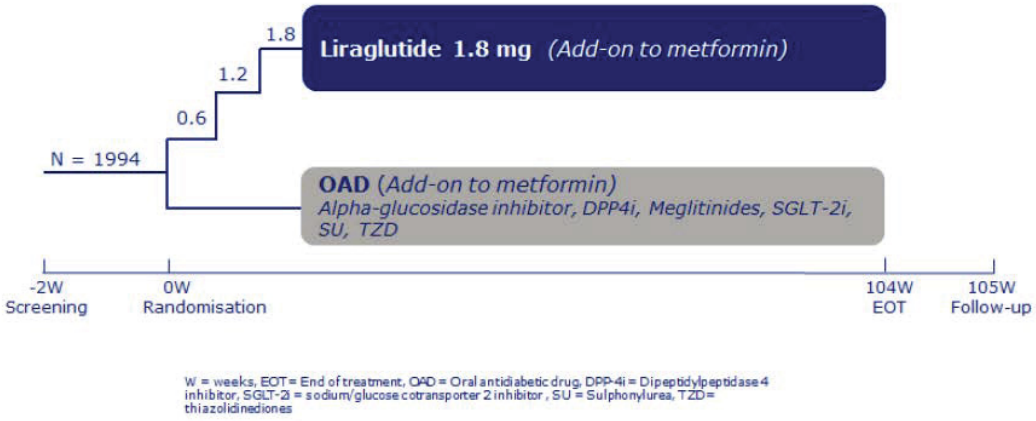
2.2 Protocol design in relation to ADaM concepts

The trial is a 104-week, randomised, phase 4, two-arm, open-label, active-controlled, multicentre, multinational, parallel-group trial, comparing the efficacy in controlling glycaemia with Victoza® as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes treated in primary care setting, inadequately controlled with metformin monotherapy.

Subjects will be randomised in a 1:1 manner to receive a once daily dose of liraglutide 1.8 mg or OAD (i.e. Alpha-glucosidase inhibitors, Dipeptidyl peptidase 4 (DPP-4) inhibitors, Meglitinides, Sodium/glucose cotransporter 2 (SGLT-2) inhibitors, Sulphonylureas and Thiazolidinediones will be chosen at the discretion of the investigator) applying the standard dose escalation for liraglutide with 0.6 mg/day with subsequent dose according to approved local label up to final dose of 1.8 mg/day at the discretion of the investigator. Subjects randomised to the OAD arm must remain on the same OAD throughout the trial. After randomisation, subjects must remain on the same antidiabetic drugs throughout the trial.

Metformin is considered background medication. The background metformin treatment must be maintained at the pre-trial dose and frequency during the entire trial treatment period unless there is a safety concern.

The maximum overall duration of the trial participation including screening and follow-up will be 105 weeks: the trial includes a 2-week screening period, followed by 104 weeks of treatment and a 1-week follow-up period after end of treatment.



APHASE	APHASEN	APERIOD	APERIODC
Screening	10		
Treatment	30	30	Treatment
Follow-up	90		

2.3 Period definitions and transitions

2.3.1 Transition rules

The treatment period defined in APHASE and APERIODC are aligned. For all datasets the APHASE and APERIOD are linked to visit dates, except for all datasets not related to visits, e.g. ADAE, and ADHYPO, where the treatment periods are linked to the treatment emergent definition. See with transition rules below Table 4.

Table 4 Transition rules for each period in APHASE

APHASE	Period ID	Transition Rules linked to visits		Transition rules linked to AEs and Hypos	
		Start	End	Start	End
Screening	SCREENING	Date of screening visit	Date of first occurring visit after the screening visit	Date of screening visit	Date of first occurring visit after the screening visit

			minus 1 day.		minus 1 day.
Treatment	Liraglutide 1.8 mg OAD (see section 8)	Date of randomisation visit.	Date of last visit in treatment period	Start date on randomised trial product	End date on randomised trial product+x days; 7 days for AEs and 1 day for hypos
Follow-up	FOLLOW-UP	Date of last visit in treatment period plus 1 day	Visit date for follow-up 1.	End date on randomised trial product+y days; 8 days for AEs and 1 day for hypos	Visit date for follow-up.

2.3.2 In-trial period

The in-trial observation period is data collected in the time period from randomisation until:

- The final planned visit for subjects who did not die or withdraw consent and was not lost to follow-up.
- The time of death for subjects who die before the final planned visit.
- The time of withdrawal for subjects who withdraw their informed consent.
- The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up.

The end date of the in-trial period will be in the variable EOSDT.

The variable INTRFL will be used to define all records in the trial period. INTRFL will be in all datasets with visit structure (BDS).

All baseline assessments (ABLFL = “Y”) eligible for analyses and taken prior to trial product initiation will be included in in-trial period (INTRFL = “Y”).

2.3.3 On-treatment period

In accordance with protocol on-treatment definition as follows: the on-treatment period is defined as the observations occurring from when subject initiates randomised treatment (treatment start date) to

- Efficacy parameters, safety lab and hypos: 1 day after last dose of randomised treatment (both days included)
- AEs: 7 days after last dose of randomised treatment (both days included)

For missing date of last dose see section 3.6.1.

For subjects in the safety analysis set (SAFFL = "Y"), the baseline assessments (ABLFL = "Y") in the in-trial period (INTRFL = "Y") will be included in the on-treatment period (ONTRTFL = "Y").

The variable ONTRTFL are used to define periods on-treatment. ONTRTFL will be 'Y' for all records in the period on-treatment and 'N' at other periods. The ONTRTFL will be included in all datasets with visit structure (BDS).

3 Analysis considerations related to multiple analysis datasets

3.1 Comparison of SDTM and ADaM content

Screening failures

Subject information, demographics and reason for violation of inclusion/exclusion/randomisation criteria for screening failures are included in a separate ADAM dataset ADSLSF. Other data from screening failures will not be included in ADAM datasets, but can be found in SDTM datasets.

A screening failure is defined as a subject withdrawn before randomisation and without any investigational medical product intake.

Age

Age is calculated based on birth date and a given visit and described in variables related to AAGE (refer section 3.6.7).

3.2 Core variables

Core variables include treatment assignments, key demographic variables and baseline assessments incl. baseline value of primary endpoint and confirmatory secondary endpoints. Baseline value of non-confirmatory endpoints will not be considered core.

The core variables are the following:

Table 5 Core variables in NN2211-4232

Variable name	Variable description
STUDYID	Study identifier used for this protocol
USUBJID	Unique subject identifier
SUBJID	Subject identifier
SITEID	Site identifier
REGION1	Geographic region 1
REGION1N	Geographic region 1 (N)
COUNTRY	Country
AGE	Age from SDTM
AGEU	Age unit from SDTM
AAGE	Derived age
AAGEG1BL	Age group 1
AAGEG1BN	Age group 1 (N)
SEX	Gender

Variable name	Variable description
RACE	Race
RACEOTH	Race other
ETHNIC	Ethnicity
RANDDT	Date of Randomization
TRTSDT	Date of First Exposure to Treatment
TRTEDT	Date of Last Exposure to Treatment
RANDFL	Randomized population flag.
FASFL	Full analysis set flag. 'Y' indicates inclusion in the set.
SAFFL	Safety analysis set flag. 'Y' indicates inclusion in the set.
TRTP	Planned treatment
TRTPN	Planned treatment (N)
TRTA	Actual treatment [conditional]
TRTAN	Actual treatment (N) [conditional]
HBA1CBL	Baseline HbA1c (%)
HBA1CSBL	Baseline HbA1c (mmol/mol)
DIABDURY	Duration of Diabetes (years)
SMOKER	Smoking Status

3.3 Treatment variables

The subject level treatment variable TRT30P represents the randomised (planned) treatment for the period "treatment" and can be found in the ADSL dataset.

In all other ADAM datasets, the record level treatment variable, TRTP is used. TRTP should be non-missing showing randomised treatment.

The values of the individual treatment variables are given in Table 6.

Table 6 Values for treatment variables

Treatment variable	Pre-specified values (based on naming from previous trials)
ARM	Liraglutide 1.8 mg, OAD
TRT30P/ TRTP	Lira 1.8 mg, OAD
TRTPN	1, 2

Note that ARM is defined as "Label" in the MMA and TRT30P is defined as "Short label" in MMA.

3.4 Subject issues that require special analysis rules

This section should include descriptions of any situation that affects the analysis of an individual subject and how it was handled. A sub-section should only be included in case a violation in the given subsection is done

Guidance to handling violations is given below:

3.4.1 Subjects receiving wrong treatment

The subject receiving treatment different than from the randomised treatment will be included in his randomised treatment arm for efficacy analysis and in the treatment received arm for safety analysis.

The subject randomised in OAD arm and switching to a different OAD during the course of trial will be considered in the OAD he started with after randomisation for all analyses.

3.4.2 Subjects randomised but not exposed to trial product

The subjects are included in the full analysis set, but excluded from safety analysis set (SAFFL='N'), and in e.g. the ADAE dataset there will not be any events in the treatment period.

3.4.3 Subjects excluded from the full analysis set

The subjects listed below are excluded from full analysis set for the reasons mentioned.

Table 7 Subjects excluded from full analysis set

Site	Subject ID	Reason for exclusion
[redacted]	[redacted]	For this subject, casebooks are not signed with the legally binding PI signature according to the ALCOA(C) principles as the site is closed due to death of the PI
		For this subject, casebooks are not signed with the legally binding PI signature according to the ALCOA(C) principles as the site is closed due to death of the PI
		For this subject, casebooks are not signed with the legally binding PI signature according to the ALCOA(C) principles as the site is closed due to death of the PI
		For this subject, casebooks are not signed with the legally binding PI signature according to the ALCOA(C) principles as the site is closed due to death of the PI
		For this subject, casebooks are not signed with the legally binding PI signature according to the ALCOA(C) principles as the site is closed

		due to extenuating circumstances
[redacted]		For this subject, casebooks are not signed with the legally binding PI signature according to the ALCOA(C) principles as the site is closed due to extenuating circumstances

3.4.4 Subjects switching sites

Subjects switching sites will keep their original subject ID and site and will be analysed accordingly.

3.5 Use of visit windowing, unscheduled visits, and record selection

The analysis flag ANELFL is used to define records selected for summaries and analyses. E.g. if several measurements exist for a parameter at a visit then ANELFL will be 'Y' for the measurement used for analysis and ' ' for the other measurements. The variable ANELREA will be filled in with a description for all ANELFL=' ' and kept empty when ANELFL='Y'.

The ANELFL and ANELREA will be included in all datasets with visit structure (BDS datasets). The ANELFL is created before deriving other flags as e.g. baseline flag to ensure only one baseline measurement for a given parameter.

3.5.1 Visit windowing or reallocation

Visit reallocation will not be performed. All data will be used for all analyses.

3.5.2 Re-test

See PSPS version 1.0 for general rules.

For the following assessment tests and re-tests the subjects are required to be fasting according to the protocol:

- Fasting plasma glucose (FPG) at visits: 2, 4, 6, 8, and 12

If these assessments are taking with fasting status 'Not fasting' the values are considered not valid (ANELFL = '').

3.6 Imputation and derivation methods

All imputations of AVAL are indicated in the variable DTYPE at record level in all ADaM datasets.

3.6.1 Date imputations

Date and time are captured in the ISO 8601 format in SDTM and follows the pattern:

yyyy-mm-ddTHH:MM:SS.

Table 8 Date variables and related imputation methods

Description	Variable	Imputation flag	Imputation method
Treatment start date	TRTSDT	TRTSDTF	Actual date of first trail product administration or Randomisation date, whichever comes later
Treatment end date	TRTEDT	TRTEDTF	Actual date of last trial product administration or Date of last visit in on-treatment period or Date of last trial-related subj-site contact, whichever comes first
Medical history/ concomitant illness	Start	ASTDTF	MONTH: Jan DAY: 1st A missing start year will not be imputed, but for medical history the event will be classified to belong to the Screening
	Stop	AENDTF	If continuing=”No” MONTH: Dec DAY: Last day of month. If imputed date is after randomisation then Date of randomisation-1 will be used
Concomitant medication	Start	ASTDTF	MONTH: Jan DAY: 1st If imputed date is before randomisation then the Date of randomisation will be used
	Stop	AENDTF	If continuing=”No” MONTH: Dec DAY: Last day of month. If imputed date is after last day in trial then Date of last trial-related subj-site contact will be used
Adverse events	Start	ASTDTF	1st of month. If imputed date is before TRSTDT then TRSTDT date will be used
	Stop	AENDTF	Last day of month. If imputed date is after last day in trial then Date of last trial-related subj-site contact will be used If “not recovered” then AENDTF=””

Hypoglycaemic events/ Hyperglycaemic Events	Start	ASTDTF	DAY: 1st unless: (1) Event stop date is non-missing where Start date will be stop date - 1 (2) Event occurs in same month as TRSTDT, in which case TRSTDT is used TIME: 00:00 Event date is the same as first drug date then time will be time of first drug intake, if possible, or 24:00
	Stop	AENDTF	DAY: The day after hypo start date TIME: 24:00

For all date variables that can be imputed (listed in Table 8) the imputation flag can take values " " (blank), D, M and Y and are set as described below. The imputation flag variable is only included if any dates/times are imputed.

Table 3.1.3.1 Some Examples of Setting of Date Imputation Flag

Missing Elements	SDTM --DTC String	ADaM Date Value (*DT Variable)[1,2] (## indicates imputed portion)	Imputation flag (*DTF variable)
None	YYYY-MM-DD	YYYY-MM-DD	Blank
Day	YYYY-MM	YYYY-MM-##	D
Month	YYYY---DD	YYYY-##-DD	M
Month and Day	YYYY	YYYY-##-##	M
Year	--MM-DD	####-MM-DD	Y
Year and Month	----DD	####-##-DD	Y
Year and Month and Day		####-##-##	Y

[1] The ISO formats used in the ADaM Date Value column are for the purposes of illustration, and are not intended to imply any type of display standard or requirement. The DT variable is numeric and the producer will determine the appropriate display format.
[2] The indication of imputed values is not intended to imply an imputation rule or standard. For example, if the month is missing, imputation rules might specify that the collected day value be ignored so that both month and day are imputed.

3.6.2 Imputations in relation to analyses

The variable DTYPE will be used to mark imputed values. Imputation of missing data will be based on the measurements included in the analysis.

3.6.3 Missing baseline

For any missing baseline value, the last value prior to baseline visit should be used. However, any measurements assigned to a visit at or before baseline, but with an assessment date after first drug date will not be used as a baseline measurement.

The value will be assigned to the baseline visit and the record will be marked with DTYPE='LVPD' (Last Value Prior Dosing). If no value exists prior to the baseline visit, the baseline value should be kept as missing.

The values assigned to a baseline visit will be included in the in-trial period (APHASE/APERIODC="Treatment" and INTRFL='Y'), even though the sample date will be prior to randomisation.

For subjects who are randomised at another date than the randomisation visit date the randomisation date will be set to the randomisation visit date.

3.6.4 Definition of treatment/trial completers

Treatment and trial completers are defined directly in the CRF by the investigator. A subject has completed trial if subject completes 104 weeks of treatment.

3.6.5 Treatment emergent events

A Treatment Emergent Adverse Event (TEAE) is defined as an event with onset or increase in severity on or after the time of first trial product administration and no later than seven days (7 times 24 hours) after the time of last trial product administration.

A Treatment Emergent hypoglycaemic episode is defined as an event with onset on or after the time of first trial product administration and no later than one day (24 hours) after the time of last trial product administration.

If the date and datetime of the event is not missing or is partial, the exact number of hours since trial product administration is used to determine if the event is treatment emergent. This also means that an event on the same date as trial product administration will not be treatment emergent if the time of the event is before time of trial product administration.

However, if the start-date and datetime for the adverse event or hypoglycaemic episode is missing or partial, and an imputed date or datetime can result in an onset of the event that is within the treatment emergent period, then the event is defined as treatment emergent. Otherwise it is defined as non-treatment emergent. Following partial date and datetime rules should be applied:

- If the time of the event is partially observed such that only the hours are observed, the event is regarded as treatment emergent if the date and hour of the event is the same as for the trial product administration or if the treatment-emergent window extends to at least the beginning of the given hour.

- If the time (hours) of the event is missing the event is regarded as treatment emergent if it occurs on the date of trial product administration or no later than the specified amount of time after this date.

- If date is missing or partial missing the event is not regarded as treatment emergent.

3.6.6 Durations

Durations are calculated as Duration (in years) $= \frac{\text{End of period} - \text{Start of period} + 1}{365.25}$

Table 9 Duration variables and related period definitions

Duration periods	Flag	Start of period	End of period	Duration variable
Exposure		TRTSDT	TRTEDT	TRTDURY
In trial (Observation time)	INTRFL	RANDDT	EOSDT	INTRDURY
On treatment	ONTRTFL	TRTSDT	TRTEDT	ONTRDURY
Duration of AE		ASTDT	AENDT	AEDURN, AEDURU
Duration of diabetes		Diagnosis of diabetes	RANDDT	DIABDURY

3.6.7 Age

AGE is the age in SDTM, and AAGE is the calculated age:

$$AAGE = \frac{Date\ of\ visit - Date\ of\ birth\ +\ 1}{365.25}$$

The age group 1 defined by the two variables AAGEG1BL and AAGEG1BN is defined as described in Table 10.

Table 10 Definition of AAGEG1BL and AAGEG1BN

AAGEG1BL	AAGEG1BN
18 ≤ age < 45 years	10
45 ≤ age < 55 years	20
55 ≤ age < 65 years	30
65 ≤ age < 75 years	40
75 ≤ age < 85 years	50
85 ≤ age	60

The age group 2 for EudraCT is defined by the two variables AAGEG2BL and AAGEGE2BN is defined as described in Table 11.

Table 11 Definition of AAGEG2BL and AAGEG2BN

AAGEG2BL	AAGEG2BN
18 ≤ age < 65 years	10
65 ≤ age < 85 years	20
85 ≤ age	30

In the age calculation, no rounding should be done to preserve the precision of days.

3.6.8 Body Mass Index (BMI)

BMI will be calculated as: Weight(kg) / Height^2(m^2) even if the BMI is collected on the CRF.

Table 12 Definition of BMIG1BL and BMIG1BLN

BMIG1BL (kg/m^2)	BMIG1BLN
< 25	10
25 - <30	20
30 - <35	30
35 - <40	40
>= 40	50

3.6.9 Rounding

Data points stored in numeric variables in datasets will not in any circumstances be rounded. Rounding will only occur if numeric variables are converted to character information, e.g. in CTR outputs as a final step when presenting numeric data. In this case, number of decimal points will follow the table shells.

3.6.10 Fasting status

According to the protocol fasting plasma glucose (FPG) at visit 2, 4, 6, 8, and 12 are required to be taken when subjects are fasting.

Any of the above measurements taken when the subjects are non-fasting will be excluded from the analyses and have ANELFL =’’ and ANELREA=’Record was excluded due to subject being non-fasting’.

All other assessments do not require a fasting status.

3.6.11 Laboratory lower and upper limit of quantification

When laboratory data are below the lower limit of quantification (LLOQ), i.e. the collected value contains “<”, the reported value is converted to half of the LLOQ value. Laboratory values above

upper limit of quantification (ULOQ), collected value containing ">", is set to the ULOQ value. The variable DTYPE will be used to mark converted laboratory data, 'LOQHALF' and 'ULOQ'.

Any analysis imputations (see section 3.6.2) will be made on the converted numeric data.

LOQ can be identified by LB.LBORRES containing "<" or ">". The conversion should happen in ADaM by updating AVAL based on the rule and setting DTYPE = "LOQHALF" or DTYPE="ULOQ1". AVALC should be left empty for these records. LBORRES and LBORRESU should be included in the dataset for traceability.
Comment:

3.6.12 Time-to-event endpoints

3.6.12.1 Primary endpoint - Time to inadequate glycaemic control

The primary endpoint is the time to inadequate glycaemic control defined as HbA_{1c} > 7.0% (53 mmol/mol) at two scheduled consecutive visits after first 26 weeks of treatment and up to 104 weeks. First possible occurrence is at week 38.

The data will inherently be interval censored, since HbA_{1c} is only measured at the scheduled visits while subjects may reach an HbA_{1c} > 7.0% at any time between 2 visits. The possible failure times will be viewed as continuous variable which can only be observed to lie in the interval between the visit when the treatment failure is established and the previous scheduled visit.

In order to perform the analysis, interval (t1, t2] will be identified where t1 is the time of the last visit at which an event has not occurred for the subject and t2 is the time of the visit at which the event occurs.

HbA_{1c} records will be extracted from the laboratory analysis dataset (ADHBA1C) with a selection on non-missing measurements which were taken while on treatment at the scheduled visits 5, 6, 7, 8, 9, 10, 11 and 12 which correspond to weeks 16, 26, 38, 52, 65, 78, 91 and 104.

The first post-baseline HbA1c assessment was done at visit 5 (Week 16). However, for determining consecutive visits, assessments from visit 6 onwards will be considered.

Visits with only non-missing measurements of HbA_{1c} will be considered to determine whether visits are consecutive or whether a visit is the last visit on treatment. For example, if there are HbA_{1c} measurements at visit 6 and visit 8 but it is missing at visit 7, then visit 6 and 8 will be considered as two consecutive visits.

The interval (t1, t2] will be identified as below.

1) If the subject discontinued treatment before Week16, subject is censored with t1 as time of visit at Week 0 and t2 as missing.

2) If the subject discontinued treatment between Week 16 and Week 26, then subject is censored with t1 as time of visit at Week 16 and t2 as missing.
3) If the subject does not have any non-missing HbA_{1c} measurements on treatment, subject is censored with t1 as time of visit at Week 0 and t2 as missing.
4) If there are two consecutive measurements of $HbA_{1c} > 7.0\%$ taken at Week26 or later, then event has occurred with t1 as time of first measurement of $HbA_{1c} > 7.0\%$ and t2 as time of second measurement of $HbA_{1c} > 7.0\%$.
5) If last available HbA_{1c} measurement is at Week 26 or later but before Week104 and the value is > 7.0%, then the event has occurred with t1 as time of last available measurement and t2 as time of next visit. If the next visit has not happened then, t2 will be time of next planned visit as per protocol defined intervals between the visits.
6) If last available HbA_{1c} is between Week 26 and Week 104 and the value is ≤ 7.0%, then the subject is censored with t1 as time of last available measurement and t2 as missing.
7) If last available HbA_{1c} is at Week 104 and there are no consecutive visits with $HbA_{1c} >$ 7.0%, then the subject is censored with t1 as time of visit at Week104 and t2 as missing.

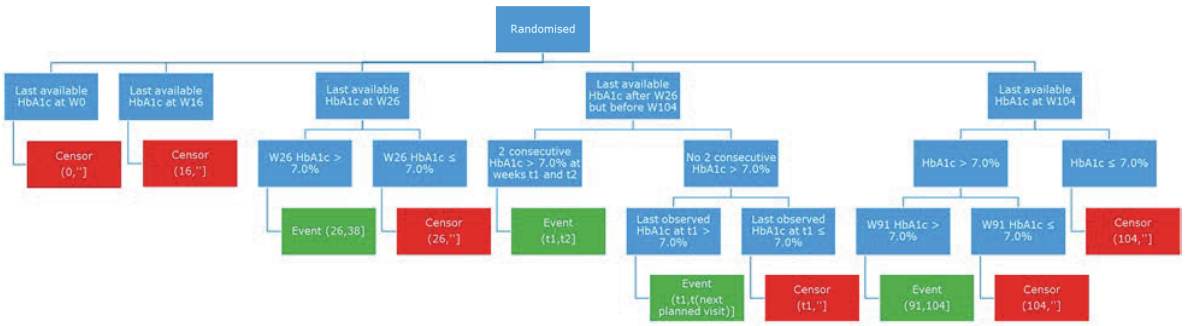


Figure 1 Identification of interval (t1, t2]

The time to inadequate glycaemic control will be compared between the Victoza® arm and the OAD arm using a two-sided non-parametric test at a 5% significance level. The test will be a generalised log rank test for interval censored failure time data, not based on any model assumptions such as proportional hazards or adjusted for any covariates.

The result of the log rank test will be presented as the asymptotic p-value obtained from a chi-square distribution.

3.6.12.2 Secondary endpoint - Time to premature treatment discontinuation (for any reason including inadequate glycaemic control)

The secondary endpoint is the time to premature treatment discontinuation (for any reason including inadequate glycaemic control).

The data will inherently be interval censored, since the criteria for treatment discontinuation is primarily checked at the scheduled visits while subjects may have discontinued treatment at any time between 2 visits. The possible event time will be considered as a continuous variable.

For subjects that discontinued treatment before Week 104, due to inadequate glycaemic control, interval (t1, t2] will be identified as mentioned in the section 3.6.12.1 .

For subjects that discontinued treatment before Week 104, due to any other reason, interval (t1, t2] will be identified where t1 is the time of the last attended visit on treatment and t2 is the time of the next planned visit.

The subjects that completed the treatment for Week 104 and did not meet inadequate glycaemic control criteria before Week 104 will be considered as censored,

The time to premature discontinuation (for any reason including inadequate glycaemic control) will be compared between the Victoza® arm and the OAD arm using a two-sided non-parametric test at a 5% significance level. The test will be a generalised log rank test for interval censored failure time data, not based on any model assumptions such as proportional hazards or adjusted for any covariates.

3.6.13 Dose data categorization

The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults.

The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose.

The oral antidiabetic and Liraglutide dose data will be categorised as <=DDD and >DDD for each drug.

For Liraglutide, as per WHO, DDD is 1.2 mg.

For Metformin, 1500 mg will be considered as DDD and doses will be categorised as <DDD and >=DDD.

Values of DDD mentioned below are taken from WHO website. Please refer to https://www.whocc.no/ddd/definition_and_general_considera/ for more information.

Table 13 Defined daily dose for oral antidiabetics

Type of OAD	ATC code	Name	DDD	Unit
Sulfonylureas	A10BB01	glibenclamide	7	mg
Sulfonylureas	A10BB02	chlorpropamide	0.375	g
Sulfonylureas	A10BB03	tolbutamide	1.5	g
Sulfonylureas	A10BB05	tolazamide	0.5	g
Sulfonylureas	A10BB07	glipizide	10	mg
Sulfonylureas	A10BB08	gliquidone	60	mg
Sulfonylureas	A10BB09	gliclazide	60	mg
Sulfonylureas	A10BB12	glimepiride	2	mg
Alpha glucosidase inhibitors	A10BF01	acarbose	0.3	g
Alpha glucosidase inhibitors	A10BF02	miglitol	0.3	g
Alpha glucosidase inhibitors	A10BF03	voglibose	0.6	mg
Thiazolidinediones	A10BG02	rosiglitazone	6	mg
Thiazolidinediones	A10BG03	pioglitazone AT	30	mg
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH01	sitagliptin	0.1	g
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH02	vildagliptin	0.1	g
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH03	saxagliptin	5	mg
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH04	alogliptin	25	mg
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH08	teneligliptin	20	mg
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH05	linagliptin	5	mg
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	A10BK01	dapagliflozin	10	mg
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	A10BK02	canagliflozin	0.2	g
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	A10BK03	empagliflozin	17.5	mg
Other blood glucose lowering drugs, excl. insulins	A10BX02	repaglinide	4	mg
Other blood glucose lowering drugs, excl. insulins	A10BX03	nateglinide	0.36	g

4 Analysis data creation and processing issues

4.1 Split datasets

Datasets larger than 5GB should be split

4.2 Data dependencies

4.2.1 **Execution** order

The execution order of some data derivations is crucial. The following selected data derivation rules apply in the given order:

- Partial date/time imputation.
- Laboratory LLOQ/ULOQ conversion.
- Reference range indicators
- Define ANELFL based on
    - Fasting status
    - Visit reallocation
    - Re-test
- Last observed value before or at first drug date carried forward to baseline
- Setting observation period record flags, and other period variables

In the datasets with a visit structure (BDS) there should only be one record per subject per visit per parameter after the data derivations at this time (for ANELFL='Y').

- Endpoints calculation: BMI, , hypoglycaemia etc.
- Trial specific endpoints calculation
- Calculate values for variables relative to baseline
- Imputations in relation to analyses, e.g. Last values carried forward

In case of several derivations for a given parameter at a given visit, the DTYPE will be the last derivation in the order above. The variable DDCOM will show all derivations for the given parameter and visit, as e.g. 'LOQHALF | LOCF from AVISITN=110'.

4.2.1.1 Execution order of datasets

For execution order of dataset, the below Table 14 shows the dependencies between datasets and the macros or functions applied to create the datasets.

- Data located in same batch are independent of each other.
- A batch depends on previous batches.

Table 14 Dataset dependencies and execution order

Table of data dependencies including application of macros and functions		
Batch	**Data set**	**Macros or functions applied to create data**
1	ADSL (version 1)	
	ADSLSF	
	ADHBA1C	• External NN library: GCMD.topic_cd_def • External metadata: ADM.plnd_flowch_item_coll
	ADLB	• External NN library: GCMD.topic_cd_def • External metadata: ADM.plnd_flowch_item_coll
	ADVS	• External NN library: GCMD.topic_cd_def • External metadata: ADM.plnd_flowch_item_coll
	ADEC	• External NN library: GCMD.topic_cd_def • External metadata: ADM.plnd_flowch_item_coll
2	ADSL (version 2)	
	ADHBA1C	• External NN library: GCMD.topic_cd_def • External metadata: ADM.plnd_flowch_item_coll
	ADLB	• External NN library: GCMD.topic_cd_def • External metadata: ADM.plnd_flowch_item_coll
	ADVS	• External NN library: GCMD.topic_cd_def • External metadata: ADM.plnd_flowch_item_coll

	ADEC	• External NN library: GCMD.topic_cd_def • External metadata: ADM.plnd_flowch_item_coll
	ADEX	• External NN library: GCMD.topic_cd_def
	ADAE	
	ADCM	
	ADMH	
	ADHYPO	
	ADHYPOEN	• External NN library: GCMD.topic_cd_def
	ADTRTEV	
	ADTRTVIS	• External metadata: ADM.plnd_flowch_item_coll
	AXNR	
	ADRESP	• External NN library: GCMD.topic_cd_def
	ADTTE	• External NN library: GCMD.topic_cd_def

4.3 Intermediate datasets

4.3.1 AXNR – Normal ranges lab data

Dataset containing normal ranges from the laboratory, that can be obtained from the central NN library GCMD.lab_range where lab='4232_ICON'. Normal range data will be applied in ADLB and listings.

Reference ranges for all the parameters in converted units is obtained using the SDTMMAP.SDTM_UNIT_CONVERSION dataset.

All lab parameters are identified from lab variable 'quest' uniquely corresponding to topic code and the dataset will add-on the ADaM analysis parameter variables PARAMCD, PARAM, and PARCAT1 obtained from the central NN library GCMD.topic_cd_def (see section 3.3 for definition of the variables).

4.3.2 ADTRTEV – Planned or actual treatment for events

ADTRTEV contains start and end dates for the events. It is based on the dataset SDTM.SE.

4.3.3 ADTRTVIS – Planned or actual treatment for findings

ADTRTVIS contains all the scheduled visits with start and end date and it is based on the SDTM.SV.

5 Analysis datasets descriptions

5.1 Overview

The ADAM datasets support all the statistical analyses of the efficacy and safety specified in the protocol and SPS. They are structured such that the statistical analyses can be performed with minimal programming. ADAM datasets are not generated specifically for outputs such as listings and other non-analytical displays.

5.2 Analysis Datasets

5.2.1 ADSL – Subject Level Analysis

The ADSL contains data from all randomised subjects, and the data will support all analyses, baseline characteristics, and disposition analyses. Data is built from SDTM DM and DS including also information from SUPPDM, SUPPSU, MH, SUPPMH, SV, CM, and EC.

ADSL data is built in two steps (batch 1 and 3 in Table 14). First version builds the ADSL data without baseline variables of HbA1c, FPG, BMI, weight, systolic blood pressure and diastolic blood pressure. Second step of ADSL add-on the listed baseline variables from lab (HbA1C and FPG) and vital sign assessments. Only the baseline variables in standard units is added to ADSL.

In the ADSL the date of randomisation is set to the date of visit 2, and not the randomisation date from IWRS. This has been chosen as there are some subjects with a randomisation visit (visit 2) date different from the randomisation date in IWRS.

5.2.2 ADSLSF – Subject level screening failures

The ADSLSF contains data from subjects not randomised (screening failure subjects in SDTM.DM) and reason for not being randomised.

Information from inclusion/exclusion SDTM data (SDTM.IE) is transposed and in case of multiple records per subject concatenated into an inclusion variable and an exclusion variable.

ADSLSF is the only dataset including subjects not enrolled.

5.2.3 ADAE – Adverse events analysis

ADAE contains all reported events for randomised subjects. All events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period are included. Data is built on SDTM data AE, SUPPAE, RELREC, and information from ADSL.

5.2.4 ADCM - Concomitant medication analysis

The ADCM contains all collected concomitant medication observations in SDTM.CM from randomised subjects. Information from SDTM.SUPPCM and SDTM.TS is added.

The continuation flag (CONTINFL) indicating if the concomitant medication is ongoing or not, relative to the treatment period, is set as "Y" when CM.CMENRF is equal to "ONGOING" otherwise it is set to blank.

The status relative to screening date (ASCRF) is set as "COMPLETED BEFORE" when analysis start date (ASTDT) and analysis end date (AENDT) is less than the screening date. ASCRF is set as "STARTED AFTER" when ASTDT is greater than the screening date. Finally, ASCRF is set as "ONGOING" when ASTDT is less or equal to the screening date and AENDT is greater or equal to the screening date or missing.

The status relative to baseline (ABLRF) is set as "COMPLETED BEFORE" when analysis start date (ASTDT) and analysis end date (AENDT) is less than the randomisation date (ADSL.RANDDT). ABLRF is set as "STARTED AFTER" when ASTDT is greater than the randomisation date. Finally, ABLRF is set as "ONGOING" when ASTDT is less or equal to the randomisation date and AENDT is greater than or equal to the randomisation date.

When AENDT is greater than or equal to the last visit date, ACRF or ABLRF is set to "ONGOING" based on ASTDT and AENDT is set to missing.

5.2.5 ADEX -- Exposure analysis set

The ADEX contains data of exposure to trial product for all randomised subjects. Data is built on SDTM.EX. There is an observation for each new dose for each subject.

5.2.6 ADEC -- Exposure analysis set

The ADEC contains data of exposure to trial product for all randomised subjects. Data is built on SDTM.EC and information from SDTM.SUPPEC is added. There is an observation for each new dose for each subject at each visit.

5.2.7 ADHBA1C – HbA1c

The ADHBA1C contains data for HbA1c assessments for all randomised subjects. Converted lab assessments also included in this dataset, see Appendix C.

The ADHBA1C is built in two steps and based on the SDTM datasets LB, and XL where LBTESTCD = "HBA1C", and add information from SUPPLB, AXNR, and ADBR. First version builds the complete ADHBA1C without the core efficacy and safety baseline variables. The second

version depends on the completed ADSL dataset and add-on the efficacy and safety core baseline variables.

5.2.8 ADHYPO – Hypoglycaemic episode analysis

The ADHYPO contains data on all reported hypoglycaemic episodes for randomised subjects. All events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period are included. Data is built on SDTM data XH, SUPPXH, RELREC, and information from ADSL.

The ONTRTFL defines the on-treatment period for hypoglycaemic episodes as described in section 2.3.3. The TRTEMFL defined the on-treatment period with an addition of 1 more day (section 3.6.5).

The variables ACAT1 contains the analysis category 1 of ADA hypoglycaemic classification described in protocol. Each of the ADA classification categories are also marked in the variable flags ADASYMFL, ADDOCSFL, ADPROBFL, ADPSEUFL, ADSEVFL, ADUNCLFL, ADUNNSFL.

The variables ACAT2 contains the analysis category 1of NN hypoglycaemic classification described in protocol. Each of the NN classification categories and merged categories are also marked in the variable flags NNASCOFL, NNCONFL, NNSECOFL, NNSEVFL, NNSYCOFL, NNSYSEFL, NNUNCLFL.

The date-time imputations follow the derivation rules in 3.6.1, and note that missing time information imputed to 00:00 implies that the hypoglycaemic episodes are imputed to occur during day-time.

5.2.9 ADHYPOEN – Hypoglycaemic episode analysis endpoint

The ADHYPOEN contains data on the number of treatment emergent severe hypoglycaemic episodes for all FAS subjects.

The counts are made over two periods: on-treatment or on-treatment+1 day, corresponding to ONTRFL=’Y’ and TRTEMFL=’Y’, respectively, in ADHYPO. This results in two rows per subject; one with the count for the on-treatment period with ONTRFL=’Y’ and TRTEMFL=’’ and one with the count for the on-treatment+1 day period with ONTRFL=’’ and TRTEMFL=’Y’.

A binary variable indicating whether there are >0 or 0 episodes are also included using the CRIT1/CRIT1FL structure.

Table 15 Derived hypoglycaemic endpoints

Endpoint	Topic code (PARAMCD)	Technical details
Severe hypoglycaemic episodes	HYPO_N_TE_SEVERE (SEV_HYPO)	Sum of records with ADHYPO.ADSEVFL=”Y” and ADHYPO.TRTEMFL=”Y”
Severe or blood glucose confirmed symptomatic hypoglycaemic episodes	HYPO_N_TE_NNSBCFL (HYCNFSEX)	Sum of records with ADHYPO.NNSECOFL=”Y” and ADHYPO.TRTEMFL=”Y”
Documented symptomatic hypoglycaemic episodes (ADA)	HYPO_N_TE_DOC_SYMP (DOC_HYPO)	Count of records where ADHYPO.TRTEMFL = "Y" and ADHYPO.ACAT1 = "Documented symptomatic hypoglycaemia"

5.2.10 ADLB - Lab Analysis

The ADLB contains data for safety lab assessments for lipids, biochemistry, haematology, and pregnancy test, and the efficacy lab assessments for FPG for all randomised subjects. Converted lab assessments is also included in this dataset for a list of lab assessments which have been reported in multiple units, see PSPS Appendix 4.

The ADLB is built in two steps and based on the SDTM datasets LB, XL, SUPPLB, AXNR, and information from ADBR. Data for HbA1c measurements are excluded. First version builds the complete ADLB without the core efficacy and safety baseline variables. The second version depends on the completed ADSL dataset and add-on the efficacy and safety core baseline variables.

Parameters with character values are presented in AVALC and include topic codes of urine pregnancy test and information on whether urine or blood samples were collected. All other parameters are in nature numeric and their values are presented in AVAL. For numeric values truncated by a lower or upper limit of quantification the value in AVAL is derived as described in section 3.6.11. The SDTM variable LB.LBSTRESC is kept in ADLB for traceability of all values.

The analysis eligibility flag, ANELFL, is defined in accordance with rules described in section 3.5. The parameter , fasting plasma glucose is required to be assessed when the subject is fasting. For non-fasting subjects these assessments have ANELFL =’’ (Section 3.6.10). All unscheduled (VISITNUM=29500) and non-visits (VISITNUM = 29999) have ANELFL = ‘’.

In LB data LDL measurements calculated using Friedwald equation are reported with the topic code "CALC_LDL_CHOL_SERUM". If the triglycerides were >4.52 mmol/L, then the direct LDL cholesterol measurement is reported with topic code "LDL_CHOL_SERUM". In such cases a new row in entered in ADLB with CALC_LDL_CHOL_SERUM = LDL_CHOL_SERUM and dtype as derived.

5.2.11 ADMH – Medical History Analysis

The ADMH contain all general medical history and history of diabetic complications, from SDTM.MH for randomised subjects. Information from SDTM.SUPPMH is added.

The continuation flag (CONTINFL) indicating if the concomitant medication is ongoing or not, relative to the treatment period, is set as "Y" when CM.CMENRF is equal to "ONGOING" otherwise it is set to blank.

The medical analysis records (ANL01FL) is set to "Y" when (MH.MHOCCUR = 'Y' and MH.MHPRESP = 'Y') or when CONTINFL is non-missing. Otherwise the ANL01FL is empty, where the ANL01REA states "Does not meet criteria for analysis".

The status relative to screening date (ASCRF) is set as "COMPLETED BEFORE" when analysis start date (ASTDT) and analysis end date (AENDT) is less than the screening date. ASCRF is set as "STARTED AFTER" when ASTDT is greater than the screening date. Finally, ASCRF is set as "ONGOING" when ASTDT is less or equal to the screening date and AENDT is greater or equal to the screening date.

The status relative to baseline (ABLRF) is set as "COMPLETED BEFORE" when analysis start date (ASTDT) and analysis end date (AENDT) is less than the randomisation date (ADSL.RANDDT). ABLRF is set as "STARTED AFTER" when ASTDT is greater than the randomisation date. Finally, ABLRF is set as "ONGOING" when ASTDT is less or equal to the randomisation date and AENDT is greater than or equal to the randomisation date.

An illness is defined as a concomitant illness at screening if ASCRF is equal to either "ONGOING" or "STARTED AFTER". Similarly, an illness is a concomitant illness at baseline if ABLRF is equal to either "ONGOING" or "STARTED AFTER".

5.2.12 ADVS - Vital Signs Analysis

The ADVS contains data on vital sign assessments for all randomised subjects. Converted assessments are also included in this dataset for a list of vital sign assessments which have been reported in multiple units, see Appendix C.

The ADVS is built in two steps and based on the SDTM datasets VS, XV, SUPPVS, and information from ADBR. The first step builds the complete ADVS without the core efficacy and

safety baseline variables. The second step depends on the completed ADSL dataset and adds the efficacy and safety core baseline variables.

BMI on CRF is excluded from ADVS and replaced by derived BMI. The BMI is derived at all control visits with topic code (topic_cd = "BMI_DERIVED") and DTYPE is set to "DERIVED" and where the record is set to ANELFL = "Y".

Note, that are no entries for investigator comments on the vital sign CRF forms, and therefore no ACOMNT variable included in ADVS data.

5.2.13 ADTTE – Time-to-Event Analyses

. The ADTTE contains data on time-to-event corresponding to primary and secondary endpoints.

The variables ALBNDDT and ARBNDDT are defined in section 3.6.12..

If an event is met, then the CNSR (censoring) is assigned as 0 else 1.

5.2.14 ADRESP – Responder Analysis

ADRESP contains the dichotomous endpoints calculated from observed data in ADHBA1C without any imputations.

Table 16 Parameters included in ADRESP dataset

TOPIC_CD	PARAM	PARAMCD
HBA1C_BLOOD_65	HbA1c <=6.5% (IDF)	HBA_BL65
HBA1C_BLOOD_LE70_WO_WEIGHT_GAIN	HbA1c <=7% without weight gain	HLE7WOWG
HBA1C_BLOOD_LE70_WO_TE_SEV_BG_HYPO	HbA1c <=7% without treatment emergent sever hypoglycaemic episodes or blood glucose confirmed symptomatic hypoglycaemic episodes	HLE7WOHY
HBA1C_BLOOD_LE70_WO_WEIGHT_GAIN_TE_SEV_BG_HYPO	HbA1c <=7% without weight gain and no treatment emergent severe hypoglycaemic episodes or blood glucose confirmed symptomatic hypoglycaemic episodes	HLE7WOWH

These endpoints will be derived using the last post-baseline measurements of HbA1c on treatment, last measurement of body weight taken on treatment, baseline body weight and the hypoglycaemic episodes in period from TRTSDT till Analysis Date.

AVALC will be derived as “Y” or “N” based on the criteria for each topic_cd.

6 Data conformance summary

This section will be updated in the Analysis Data Reviewers Guide.

7 Submission of Programs

This section will be updated in the Analysis Data Reviewers Guide.

8 Specification of output

See PSPS version 1.0.

9 References

Appendix A Table shells location

Table 17 Table shells location

Document	novoDOCS object ID
4232-sec-14-1-demographic-data-statistical-table-shells	[redacted]
4232-sec-14-2-efficacy-data-statistical-table-shells	
4232-sec-14-3-1-adverse-events-statistical-table-shells	
4232-sec-14-3-2-deaths-saes-statistical-table-shells	
4232-sec-14-3-4-abnormal-lab-list-statistical-table-shells	Not Applicable
4232-sec-14-3-5-lab-displays-statistical-table-shells	[redacted]
4232-sec-14-3-6-other-safety-observations-displays-statistical-table-shells	
4232-sec-14-3-7-other-safety-observations-lists-statistical-table-shells	Not Applicable
4232-sec-16-2-1-discontinued-patients-statistical-table-shells	[redacted]
4232-sec-16-2-3-patients-excluded-from-efficacy-analysis-statistical-table-shells	Not Applicable
4232-sec-16-2-4-individual-demographic-data-statistical-table-shells	[redacted]
4232-sec-16-2-5-compliance-and-drug-concentration-data-statistical-table-shells	Not Applicable
4232-sec-16-2-6-individual-efficacy-response-data-statistical-table-shells	Not Applicable
4232-sec-16-2-7-adverse-event-listings-statistical-table-shells	[redacted]
4232-sec-16-2-8-listing-individual-lab-measurements-statistical-table-shells	Not Applicable

Appendix B Good Specification Practice for Data Derivations

B.1 Sequence of ANELREA text:

The ANELREA text is prioritized in the following order:

1. "Unscheduled assessment"
2. "Assessment not planned"
3. "Record at baseline visit was excluded due to date after treatment start"
4. "Before in-trial observation period"
5. "After in-trial observation period"
6. "No measurement"
7. "Record was excluded due to subject being non-fasting"
8. "Retest rule 1: Not first value for visit"
9. "Assessment done after starting add on glucose lowering drug"

The ANELREA enters all BDS ADaM datasets.

Appendix C Table of converted units applied

Parameter	Topic code	SI unit	Conventional unit (if required)	Conversion factor (SI to conventional unit)
Total Bilirubin	T_BILIRUBIN_SERUM	umol/L	mg/dL	0.058466
Creatinine	CREATININE_SERUM	umol/L	mg/dL	0.0113118
Fasting Plasma Glucose	FPG_PLASMA	mmol/L	mg/dL	18.02
HbA1c	HBA1C_BLOOD	%	mmol/mol	<src>*10.93-23.5
HDL Cholesterol	HDL_CHOL_SERUM	mmol/L	mg/dL	38.61
Haemoglobin	HAEMOGLOBIN_BLOOD	mmol/L	g/dL	1.6125
LDL Cholesterol	LDL_CHOL_SERUM	mmol/L	mg/dL	38.61
Calculated LDL Cholesterol	CALC_LDL_CHOL_SERUM	mmol/L	mg/dL	38.61
Potassium	POTASSIUM_SERUM	mmolL	mEq/L	1
Total Cholesterol	T_CHOL_SERUM	mmol/L	mg/dL	38.61
Triglycerides	TRIGLYCERIDES_SERUM	mmol/L	mg/dL	89

10 Change Log

Edition no.	**1.0**	**Effective date:**	**10 Jun 2019**
Changes to document	First version.		
	2.0	**Effective date:**	**13 September 2019**
	Trial specific updates		