Statistical Analysis Plan H9X-IN-GBGR V2.0

A 24-week Multicenter, Open-label, Single-arm Study to Evaluate Safety in Patients With Type 2 Diabetes Mellitus in India Treated With Dulaglutide

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STATISTICAL ANALYSIS PLAN

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Glossary of abbreviations

ABBREVIATION	DESCRIPTION
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	estimated glomerular filtration rate
FBG	Fasting blood glucose
GI	Gastrointestinal
HbA1C	Hemoglobin A1c
ICH	International Conference on Harmonisation
IMP	Investigational product
LOCF	Last observation carried forward
MMRM	Mixed model for repeated measures
MedDRA	Medical dictionary for regulatory activities
N	Sample size
ODS	Output delivery system
PDF	Portable Document Format
PT	Preferred term
RTF	Rich text format
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
T2DM	Type 2 diabetes mellitus
TEAEs	Treatment-emergent adverse events
TLFs	Tables, data listings and figures
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

1. Overview

1.1 Introduction

This document describes the rules and conventions to be used in the presentation and analysis of a 24-week multicentre, open-label, single-arm study to evaluate safety in patients with type 2 diabetes mellitus in India treated with dulaglutide.

This statistical analysis plan (SAP) is based on protocol H9X-IN-GBGR, 1.0, dated 02-Jun-22.

2. Trial objectives

The following objectives are those stated in the protocol.

2.1 Primary objectives

- Assess the safety profile of 1.5 and 0.75 mg dulaglutide in patients with T2DM in India

2.2 Secondary objectives

- Change in HbA1c for pooled doses of dulaglutide

2.3 Exploratory objectives

- Change in body weight
- Change in FBG
- Change in vital signs

3. Endpoints

3.1 Primary endpoints

- Incidence of AEs (deaths, SAEs, TEAEs, and hypoglycemia, including severe hypoglycemia)
- Proportion of patients reporting AEs and SAEs between baseline and Week 24
- Incidence of GI AEs

3.2 Secondary endpoints

- Mean change in HbA1c from baseline to Week 24

3.3 Exploratory endpoints

- Mean change in body weight from baseline to Week 24
- Mean change in FBG from baseline to Week 24
- Mean change in systolic blood pressure, diastolic blood pressure, and pulse rate from baseline to Week 24

4. Trial design

4.1 Design overview

This is a Phase 4, single-arm study to study the safety of dulaglutide in patients with T2DM in India who are on stable doses of oral antihyperglycemic medications with or without stable doses of basal or premix insulin for the last 3 months prior to screening.

The study consists of below visit:

- Screening visit
- 2-week lead-in period
- 24-week treatment period, and
- Safety follow-up visit.

4.2 Schedule of events

Refer to the protocol section 1.3 for the schedule of activities.

5. Changes/deviations from the planned analysis

The statistical analysis/methods as described in the protocol were adopted. There are no changes to the planned analyses. Any deviation from original statistical analysis plan will be described and justified in the final clinical study report.

6. Analysis populations

Agreement and authorization of participants included/excluded from each analysis population will be reached prior to final database hard lock. Sponsor will review/supply a list of all participants to be excluded from the relevant analysis populations, including the reason(s) for exclusion from the analysis populations.

6.1 Enrolled Analysis Set (ENRL)

All participants who sign informed consent form and are screen positive.

6.2 Full Analysis Set (FAS)

All patients who received at least 1 dose of study treatment and have at least 1 measurement of HbA1c after study treatment.

6.3 Per-Protocol Analysis Set (PP)

All patients in the FAS who meet the following criteria

- Have no important (major) protocol deviations that could impact the assessment of the primary objective
- are at least 80% compliant with the study drug in terms of dose taken
- have no instance of deviation from persistence with study drug in terms of no more than the 15 days gap between 2 consecutive doses
- complete the treatment phase (24 weeks) for the primary endpoint

6.4 Safety Analysis Set (SAF)

All patients who received at least 1 dose of study treatment.

7. General considerations

7.1 Visit and date conventions

Visit day will be calculated from the reference start date which will be used to present start/stop day of assessments and events. The *reference start date* is defined as the date of first study treatment administration. The following conventions will be used for visit references:

- $\text{Visit day} = \text{date of Visit} - \text{reference start date}$
- $\text{Visit week} = \frac{\text{visit day}}{7},\ \text{rounding up to next whole number}$
- If event date<reference start date then event day= (date of event - reference start date), Otherwise if event date is on or after reference start date then event day= (date of event - reference start date) +1

No visit windowing (i.e., remapping of visits based on visit windows) will be performed for this trial. The assigned nominal visit will be used for by-visit summaries. Unscheduled measurements will not be included in by-visit summaries.

7.2 Baseline

Baseline is defined as the last non-missing observation made prior to the first treatment administration.

7.3 Stratifications

In general, the treatment will be presented as overall strata (i.e., Dulaglutide treatment group).However if more than 20% of the subjects undergo dose modification/downgrade or receive only 0.75 mg dose during the trial, then separate strata will be presented apart from overall: subjects with 1.5 mg only, subjects with any dose modification (at least one dose of 1.5 mg and at least 1 dose of 0.75 mg) and subjects with 0.75 mg only if they constitute more than 20% of the enrolled population. If 0.75 mg only group constitutes less than or equal to 20% of enrolled population then it can be clubbed together with the dose modified group.

Note: The dose modification may not be applicable for those who start on 0.75 mg and upgrade to 1.5 mg.

Subgroup analysis will be done on the primary, secondary, and exploratory data based on the below stratification:

- age (<65 year and ≥65 year)
- HbA1c (<8.5 and ≥8.5)
- Sex (Female and male)
- BMI category (<27 kg/m^2) and ≥ 27 kg/m^2)

7.4 Statistical tests

Unless otherwise specified, testing effect of dulaglutide on change from baseline will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided.

The mixed model for repeated measures method, Negative binomial models, and Cox proportional hazard models techniques will be used.

7.5 Common calculations

Change from baseline will only be calculated for patients with both baseline and post baseline values as:

Change from baseline = postbaseline value – baseline value

7.6 Software

All analyses will be conducted using SAS® Version 9.4 or later.

8. Statistical considerations

8.1 Multicentre studies

The study will be conducted at multiple centres in India.

8.2 Missing data

For the actual value and change from baseline, a descriptive analysis using LOCF will be performed, using the baseline or 12-week value, if the 24-week value is missing or occurred after use of rescue medication. While performing the mixed modelling with repeated measures (MMRM) Missing data will be assumed missing at random and will be accommodated by the MMRM.

If convergence is not met in the MMRM, the change in HbA1c level from baseline to Week 24 will be analysed using the general linear model and The LOCF method of missing value imputation will be used.

If none of the models converge then an analysis of covariance using LOCF imputation with similar terms as in the MMRM (except no terms that include visit) will be used in its place for body weight, fasting blood glucose, systolic blood pressure, diastolic blood pressure and pulse rate.

9. Output presentations

The templates provided in the separate output templates document describe the format and content for presentation of tables, listings, and figures (TLFs).

Summary statistics will be provided for the observed value and change from baseline will be summarized.

Unless otherwise specified, testing effect of dulaglutide on change from baseline will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided.

For continuous measures, summary statistics will include number of patients, mean, SD, median, minimum, maximum, and interquartile ranges for both the actual and the change from baseline measurements. Number of missing values will be specified along with this information.

For categorical measures, summary statistics will include sample size, frequency, and percentages. Number of missing values will be specified along with this information.

10. Participant disposition and withdrawal

10.1 Variables and derivations

The trial classifications are defined as follows:

- Screening failure:

  Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after 4 weeks from the date of screen failure after discussion with the medical monitor.

- Completed trial:

  A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit.

- Lost to follow-up:

  A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. For participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site, the site personnel or designee is expected to make diligent attempts to contact till 4 weeks from the scheduled visit.

The following parameters will be summarised for the subject's disposition table as per eCRF:

- Number of total screened subjects
- Number of screen failure subjects
- Reason of screen failure subjects
- Number of screen positive subjects
- Subjects who are screened positive but did not receive treatment
- Number of Subject's in Enrolled Analysis set
- Number of Subject's in Full Analysis set
- Number of Subject's in per-protocol analysis set
- Number of Subject's in safety analysis set
- Number of subject's completed trial

- Number of Subject's Completed All Weekly Doses Within Treatment Period
- Number of subjects received 1.5 mg only
- Number of subjects received 0.75 mg only
- Number of subjects with any dose modification* (* subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg)
- Number of subjects withdrew early prior to receiving treatment
- Number of subjects withdrew early from trial
- Subjects who are screened positive but did not receive treatment

The following parameters will be summarised for the early withdrawals table as per eCRF Subject's primary reason for discontinuation (reasons mentioned in eCRF "End of the Study" form) which is as follows:

- Adverse event
- Death
- Lost to follow-up
- Pregnancy
- Protocol violation
- Screen failure
- Consent withdrawal not due to an adverse event
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by sponsor
- Migration from the study site such that follow up visits are not possible
  Other

10.2 Analysis

Population:	ENRL
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3: a. Subjects on 1.5 mg only b. Subjects on 0.75 mg only c. Subjects with any dose modification*

	* Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg Listing: By subject
Statistics:	Participant's disposition and Withdrawal will be summarised frequency and percentages and the screen, screening failure subjects will be summarised (frequency) by total for table. The listing will be provided. Protocol deviations will be summarised and presented in listing.

11. Participant demographics and other baseline characteristics

11.1 Variables and derivations

The following demographic and other baseline characteristics will be summarized:

- Age (Years)
- Gender
- Race
- Ethnicity
- Height (cms) at Screening
- Weight (kgs) at Screening
- BMI (kg/m^2) at Screening

11.2 Analysis

Population:	FAS
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3: a. Subjects on 1.5 mg only b. Subjects on 0.75 mg only c. Subjects with any dose modification* * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg Listing: By subject
Statistics:	Baseline and Demographic variables will be summarized and listed. Overall summaries will include descriptive statistics for continuous measures (number of patients, mean, SD, median, minimum, maximum, interquartile ranges, number of missing values) and for categorical measures (sample size, frequency, and percentages and number of missing values). The listing will be presented for diabetes diagnosis data at screening. Summary of duration of type 2 diabetes and associated baseline treatment will be presented.

12. Exposure and Compliance to the treatment

12.1 Variables and derivations

The date of first treatment administration will be derived as the first date of dosing from the exposure eCRF page.

The following parameters will be presented for the exposure summary:

- Number of subjects received first dose
- Number of subjects received weekly doses by each visit
- $Duration\ of\ exposure\ (days) = (Date\ of\ last\ treatment\ administration - Date\ of\ first\ treatment\ administration) + 1$

Compliance will be calculated as follows:

- Compliance with the study treatment (%) = (Actual Dose/ Planned Dose)*100

12.2 Analysis

Population:	SAF
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3: a. Subjects on 1.5 mg only b. Subjects on 0.75 mg only c. Subjects with any dose modification* * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg Listing: By subject and visit
Statistics:	The exposure and compliance to the treatment will be summarised and listing will be presented. A plot of dose over time (weeks) per subject will be presented. Listing for deviation from persistence will be provided for the patients who had more than 15 days of gap between two consecutive doses and corresponding dose number.

13. Medical history

13.1 Variables and derivations

Medical history will be coded using the MedDRA central coding dictionary Version (refer to DMP for dictionary version).

Partial date imputation is not done for medical history.

The following parameters will be summarised for the subject's medical history:

- Number of subjects with at least one medical history
- Number of subjects for each medical history by SOC and PT

13.2 Analysis

Population:	SAF and PP
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3: a. Subjects on 1.5 mg only by Primary SOC and PT in decreasing order b. Subjects on 0.75 mg only by Primary SOC and PT in decreasing order c. Subjects with any dose modification* by Primary SOC and PT in decreasing order * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg Listing: By subject
Statistics:	Medical history will be summarised (frequency and percentages) for table and listing also be presented.

14. Prior and concomitant medications

14.1 Variables and derivations

All medications will be coded using the WHO-DD, dated (refer to DMP for dictionary date) All concomitant therapies that was originally mapped using the WHO Drug Dictionary in the ClinTrial database will be further classified using Anatomical Therapeutic Chemical (ATC) codes for reporting purposes.

'Prior medications' are defined as any medication taken prior to first administration of the study treatment.

'Concomitant medications' are defined as any medication taken after or on the day of first administration of the study treatment.

In section 23 Appendix 1 the algorithm is given for calculation of partial date imputation for prior and concomitant medications, and it will be used for partially missing prior and concomitant medications, start and end date imputation.

The following parameters will be summarised separately for each sub-categories (General concomitant medications, rescue therapy and drug used in diabetes) as prior and concomitant medications:

- Number of subjects with at least one prior and concomitant medication
- Number of subjects for each prior and concomitant medication by ATC and PT.

14.2 Analysis

Population:	SAF and PP
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3: a. Subjects on 1.5 mg only by ATC and PT b. Subjects on 0.75 mg only by ATC and PT c. Subjects with any dose modification* by ATC and PT * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg Listing: By subject

Statistics: Prior and concomitant medication will be summarized separately as (frequency, percentages) for table and listing will be presented.

15. Adverse events

15.1 Variables and derivations

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version (refer to DMP for dictionary version).

For the definition of Adverse events (AE) and Serious adverse event (SAE) refer to the protocol section 10.3.

TEAEs are defined as events that are newly reported after the first study drug treatment or are reported to have worsened in severity after the first study drug treatment.

In section 24 Appendix 2 the algorithm is given for calculation of partial date imputation for adverse events (AEs), and it will be used for partially missing adverse event start and end date imputation.

The following parameters will be summarised for the overview of participants' adverse events:

- Any AEs
- Any TEAEs
- Related TEAEs
- Severity of TEAEs (Mild, Moderate, Severe, Life threatening and Death)
- Outcome of AEs (Recovered or resolved, Recovering, or resolving, Not recovered or not resolved, Recovered, or resolved with sequelae, Fatal and Unknown)
- Serious AEs
- AEs leading to Discontinuation from the study
- AEs leading to Death
- Related AEs leading to Death

15.2 Analysis

An overview summary will be presented for TEAEs and SAEs as (n=number of subjects, m=number of events and %=percentage of subjects) by treatment i.e., Dulaglutide, using SAF population.

The listings of Pre-treatment AEs, TEAEs, Serious AEs and AEs resulting in death and AEs leading to study discontinuation will be presented, using SAF population, by treatment group and subject number. AEs will be listed by subject, SOC, Medical Dictionary for Regulatory Activities® PT, severity, outcome, and relationship to the study drug, or procedure for all subjects.

Note: If there are uncoded adverse events, then the uncoded category will be added in the AEs by SOC/PT summary tables.

15.2.1 Incidence of TEAEs, Drug-related TEAE, Serious adverse events (SAEs) and AEs leading to death

Population: SAF and PP

Stratification: Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3:

a. Subjects on 1.5 mg only by Primary SOC and PT in decreasing order

b. Subjects on 0.75 mg only by Primary SOC and PT in decreasing order

c. Subjects with any dose modification* by Primary SOC and PT in decreasing order

* Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg

Statistics: Treatment emergent AEs, Drug-related TEAE, Serious adverse events (SAEs) and AEs leading to death will be summarized as (n=number of subjects, m=number of events and %=percentage of subjects) for table.

15.2.2 TEAEs and Serious AEs by severity

Population: SAF and PP

Stratification: Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3:

a. Subjects on 1.5 mg only by Primary SOC and PT in decreasing order and Severity

b. Subjects on 0.75 mg only by Primary SOC and PT in decreasing order and Severity

c. Subjects with any dose modification* by Primary SOC and PT in decreasing order and Severity

* Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg

Statistics: Treatment emergent AEs and Serious adverse events (SAEs) by severity will be summarized as (n=number of subjects, m=number of events and %=percentage of subjects) for table.

16. Safety laboratory tests

16.1 Variables and derivations

All laboratory parameters mentioned in protocol section 10.5 will be summarized.

Quantitative laboratory measurements reported as "< X", i.e., below limit of quantitation, or "> X", i.e., above the upper limit of quantification, will be converted to X for quantitative summaries, but will be presented as recorded, i.e., as "< X" or "> X" in the data listings.

16.2 Analysis

Population: SAF and PP

Stratification: Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3:

a. Subjects on 1.5 mg only

b. Subjects on 0.75 mg only

c. Subjects with any dose modification*

* Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg

Listing: by subject, visit and each laboratory test parameter

Statistics: Summaries of all the laboratory tests will include descriptive statistics of the following:

- Actual and change from baseline (number of patients, mean, SD, median, minimum, maximum, and interquartile ranges) (for quantitative measurements)
- Frequencies and percentages (n and %) (for qualitative measurements)

All the laboratory tests will be listed separately and listing of abnormal laboratory test will be presented.

Continuous chemistry and hematology measures will be summarized as change from baseline to Week 24 using the general linear model, with the baseline value of the response variable as covariate and the estimate and 95% CI will be presented. In addition, a descriptive analysis for actual value and change from baseline will be performed

using LOCF. It will be performed using the baseline or 12-week value, if the 24-week value is missing.

17. Vital signs

17.1 Variables and derivations

The following vital signs will be reported for this study:

- Weight (in Kgs)
- Diastolic Blood Pressure (mmHg)
- Systolic Blood Pressure (mmHg)
- Pulse (beats per minute)
- Temperature

17.2 Analysis

Population:	SAF and PP
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3: a. Subjects on 1.5 mg only b. Subjects on 0.75 mg only c. Subjects with any dose modification* * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg Listing: by subject, visit and each vital sign parameter
Statistics:	The vital signs except temperature will be summarised as actual and change from baseline (number of patients, mean, SD, median, minimum, maximum, and interquartile ranges) for table. The listing will be presented for all vital sign parameters. Mean ± SD plot will be provided for Vital sign parameters.

18. Primary endpoint

18.1 Incidence of AEs (deaths, SAEs, TEAEs, and hypoglycemia, including severe hypoglycemia)

18.1.1 Variables and derivations

Variables:

- All AEs will be captured in the “Adverse Events” eCRF form.
- Hypoglycemia events will be captured in the “Hypoglycemic events” eCRF form.

Derivations:

- To identify incidence of deaths the eCRF question “the severity of the adverse event” = “Death” will be used from AE form.
- If the questions “the adverse event serious” is indicated as “Yes” then corresponding events will be considered as SAEs.
- If the AE started on or after the first treatment administration date will be considered as TEAEs.
- Hypoglycemia events will be captured and identified using the “Hypoglycemic events” eCRF form.
- If the question “Did subject have any Hypoglycemic events” is “Yes” on “Hypoglycemic events” eCRF form and the questions “the adverse event serious” is indicated as “Yes” on the AE eCRF form, then corresponding events will be considered as severe hypoglycemia events.
- The incidence of AEs= Number of new AEs post intervention/Total eligible population *100.
- The incidence of hypoglycemic AEs= (Number of new hypoglycemic AEs post intervention/Total eligible population)*100.
- Number of hypoglycemic events per patient-year (365.25 days)= Number of patients with hypoglycemic events /365.25
- Exposure Adjusted AE Incidence= Number of patients with new or worsened AEs during treatment period / (Patient-year exposure/365.25)
- Patient-year exposure is counted in days up to the AE (or end of time at risk for subjects without AE).

18.1.2 Analyses

Population:	FAS and PP
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3: a. Subjects on 1.5 mg only b. Subjects on 0.75 mg only c. Subjects with any dose modification* * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg Listing: by subject and events
Statistics:	The incidence of AEs (including deaths, SAEs, TEAEs, hypoglycemia, including severe hypoglycemia and GI disorders) will be summarised as frequency and percentages. The listings will be presented for the hypoglycaemia events. The incidence of AE (death, SAE, and TEAE) will be summarized. The rate per year (i.e., number of deaths, SAE, and TEAEs per subject per year over the study period) will be assessed using a negative binomial model with the log of the study treatment exposure time as an offset variable and the model will be performed as per details mentioned below. The incidence of hypoglycemic AEs will be summarized. The number of hypoglycemic events per subject over the study period will be analysed as continuous variables and will be summarized as (n, mean, standard deviation, standard error, median, minimum, maximum). The rate per year of hypoglycemic events, that is, the number of hypoglycemic events per patient-year (365.25 days) will be assessed using a negative binomial model, with baseline HbA1c and baseline insulin usage as covariates and the log of the study treatment exposure time as an offset variable.

The Negative Binomial Model i.e., the generalized linear model will be used with baseline HbA1c and baseline insulin usage and the log of the study treatment exposure time as offset variable.

The incidence rate, least square mean and corresponding 95% confidence interval will be provided for table.

Also, in case we have more than 20% data missing in any of the covariate, we will repeat the analysis after omitting the impacted covariate.

In case of multiple doses of insulin uptake per day, a sum of insulin per day will be used as the baseline insulin covariate. Regimen for subjects with more than 1 regimen type per day will be reviewed by

medical team. Insulin Dose level for subjects not on insulin will considered as 0 and the corresponding regimen as 'Non'.

In case convergence is not met with the above variables, only baseline HbA1c and baseline insulin usage(Yes/No) will be considered.

Exposure-adjusted AE incidence will be presented by the severity and preferred term for the primary analysis.

Additionally, all the analysis will be repeated for the below mentioned subgroups:

- age (<65 year and ≥65 year)
- HbA1c (<8.5 and ≥8.5)
- Sex (Female and male)
- BMI category (<27 kg/m^2) and ≥ 27 kg/m^2)

18.2 Proportion of patients reporting AEs and SAEs between baseline and Week 24

18.2.1 Variables and derivations

Variables:

- All AEs and SAEs will be captured in the "Adverse Events" eCRF form.

Derivations:

- AE and SAE occurred between visit Baseline Visit 2 (week 0) and Visit 8 (week 24) will be used.

18.2.2 Analyses

Population:	FAS and PP
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3: a. Subjects on 1.5 mg only by Primary SOC and PT in decreasing order b. Subjects on 0.75 mg only by Primary SOC and PT in decreasing order

c. Subjects with any dose modification* by Primary SOC and PT in decreasing order

* Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg

Statistics: The proportion of patients with at least one AEs, TEAEs, and SAEs occurring within the duration of the study (24 weeks) after being administered dulaglutide 1.5 or 0.75 mg will be presented followed by primary SOC and PT. Frequency, percentage and corresponding 95% confidence interval will be provided for table. 95% CI is calculated using exact binomial method (Clopper-Pearson method) for single proportions for the incidence of total adverse events and serious adverse events. Additionally, all the analysis will be repeated for the below mentioned subgroups:

- age (<65 year and ≥65 year)
- HbA1c (<8.5 and ≥8.5)
- Sex (Female and male)
- BMI category (<27 kg/m^2) and ≥ 27 kg/m^2)

18.3 Incidence of gastrointestinal (GI) AEs

18.3.1 Variables and derivations

Variables:

- All gastrointestinal (GI) AEs will be captured in the “Adverse Events” eCRF form.

Derivations:

- If the adverse event preferred terms (PT) are coded as “Nausea, Vomiting and Diarrhoea” and system organ class (SOC) are coded as “Gastrointestinal disorders” then corresponding adverse events will be considered as gastrointestinal (GI) AEs for primary analysis. Any additional PT under GI may be added as per medical review before final analysis. However, all AE terms that get coded under GI as per medical dictionary or medical review will be considered as GI for safety analysis.

18.3.2 Analyses

Population:	FAS and PP
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3: a. Subjects on 1.5 mg only b. Subjects on 0.75 mg only c. Subjects with any dose modification* * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg
Statistics:	The incidence of GI AEs will be summarised and a plot of prevalence by severity (mild, moderate, or severe) for nausea, vomiting, and diarrhoea over the 24-week period will be provided for the rate of GI AEs. Plot of severity with reference to time will be provided by subjects. Three Cox proportional hazard models, each with covariates for baseline HbA1c and baseline insulin use, will be used to model the time to the first onset of nausea, vomiting, or diarrhoea TEAE,

respectively. Hazard ratio and 95% confidence interval and p-value will be presented for the covariates for the overall data. If additional analysis based of dose stratification is done, the Hazard ratio and 95% confidence interval and p-value will also be presented for dose with 1.5 mg as the reference group.

Subjects who do not experience any GI AEs during 24 weeks and discontinued before 24 weeks of period will be considered as censored.

The Kaplan Meier plot (unadjusted) will be presented for median time to first onset of nausea, vomiting, or diarrhoea TEAE, respectively along with corresponding 95% confidence interval. Y axis will represent the survival probability of the GI AEs and X axis will represent the duration in days of GI event occurred from first dose administration. Number of subjects at risk will be presented in the plot.

Additionally, all the analysis will be repeated for the below mentioned subgroups:

- age (<65 year and ≥65 year)
- HbA1c (<8.5 and ≥8.5)
- Sex (Female and male)
- BMI category (<27 kg/m^2) and ≥ 27 kg/m^2)

19. Secondary endpoint

19.1 Mean change in HbA1c from baseline to Week 24

19.1.1 Variables and derivations

Variables:

- HbA1c results

Derivations:

- HbA1c results between visit baseline visit 2 (week 0) and visit 8 (week 24) will be used.

19.1.2 Analyses

Population:	FAS and PP
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population as per section 7.3: a. Subjects on 1.5 mg only b. Subjects on 0.75 mg only c. Subjects with any dose modification* * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg
Statistics:	The mean change in HbA1c level from baseline to Weeks 12 and 24 for all available data including post-rescue medication values will be analysed using descriptive statistics (mean, median, SD, SE, minimum, maximum, and number with missing values). In addition, for the actual value and change from baseline, a descriptive analysis using LOCF will be performed, using the baseline or 12-week value, if the 24-week value is missing or occurred after use of rescue medication. For subjects requiring rescue medication, HbA1c values recorded after the first administration of rescue medication will not be

considered for analysis, and these values will be considered as missing.

Note: Rescue medications will be identified by the medical team.

The MMRM will be used for analysis of the change in HbA1c level from baseline to Weeks 12 and 24. An unstructured covariance structure will be used to model the within-patient variability and implicitly adjust for missing data. If this analysis fails to converge, the following covariance structures will be tested in order.

1. Toeplitz with heterogeneity
2. Autoregressive with heterogeneity, by visit
3. Compound symmetry with heterogeneous variances, by visit 4. Toeplitz
5. Autoregressive
6. Compound symmetry without heterogeneous variances, by visit

From the above covariance structures, the first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares mean using Type III sum of squares.

The MMRM for each of the endpoints will include the respective baseline score and any covariates. Baseline insulin level, insulin regimen and insulin use(yes/no) will be included as covariates in the model if convergence is met. If convergence is not met with baseline insulin level and insulin regimen as covariates, then only insulin use(yes/no) will be used.

If convergence is not met in the MMRM, the change in HbA1c level from baseline to Week 24 will be analysed using the general linear model. The general linear model will evaluate the change from baseline in HbA1c level as the dependent variable and the

baseline value of HbA1c as covariate. The LOCF method of missing value imputation will be used.

Additionally, all the analysis will be repeated for the below mentioned subgroups:

- age (<65 year and ≥65 year)
- HbA1c (<8.5 and ≥8.5)
- Sex (Female and male)
- BMI category (<27 kg/m^2) and ≥ 27 kg/m^2)

Forest plot of Mean change from baseline of HbA1c for overall and subgroup will be presented. Line plot will be plotted to show the trend of HbA1c lowering. Mean change values will be used by timepoint for plotting.

20. Exploratory endpoint

20.1 Mean change in body weight from baseline to Week 24

20.1.1 Variables and derivations

Variables:

- Weight (in Kgs)

Derivations:

- Weight (in Kgs) results between visit baseline visit 2 (week 0) and visit 8 (week 24) will be used.

20.1.2 Analyses

Population:	FAS and PP
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population: a. Subjects on 1.5 mg only b. Subjects on 0.75 mg only c. Subjects with any dose modification* * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg
Statistics:	The actual values and change from baseline will be summarized by descriptive statistics (n, missing values, mean, median, SD, SE, minimum, and maximum) by visit. No multiplicity adjustment will be done. The analysis of Mean change in weight at 24 weeks will use the MMRM. Missing data will be assumed missing at random and will be accommodated by the MMRM. The MMRM using restricted maximum likelihood will be done for analyses (note: statistical comparison will not be conducted) during the entire study period. An unstructured covariance structure will be used to model the within-patient variability and implicitly adjust for missing data. If

this analysis fails to converge, the following covariance structures will be tested in order.

1. Toeplitz with heterogeneity
2. Autoregressive with heterogeneity, by visit
3. Compound symmetry with heterogeneous variances, by visit 4. Toeplitz
5. Autoregressive
6. Compound symmetry without heterogeneous variances, by visit

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares mean using Type III sum of squares.

If none of the models converge then an analysis of covariance using LOCF imputation with similar terms as in the MMRM (except no terms that include visit) will be used in its place. The model will evaluate the change from baseline in weight as the dependent variable and the baseline value of weight as covariate.

The MMRM for each of the endpoints will include the respective baseline score and any covariate. Baseline HbA1c and baseline insulin use will be included as covariate in the model if convergence is met. If convergence is not met with baseline insulin level and insulin regimen as covariates, then only insulin use(yes/no) will be used for insulin usage.

Additionally, all the analysis will be repeated for the below mentioned subgroups:

- age (<65 year and ≥65 year)
- HbA1c (<8.5 and ≥8.5)
- Sex (Female and male)
- BMI category (<27 kg/m^2) and ≥ 27 kg/m^2)

Line plot will be plotted to show the trend of body weight lowering.

Mean change values will be used by timepoint for plotting.

20.2 Mean change in FBG from baseline to Week 24

20.2.1 Variables and derivations

Variables:

- FBG results

Derivations:

- FBG results between visit baseline visit 2 (week 0) and visit 8 (week 24) will be used.

20.2.2 Analyses

Population:	FAS and PP
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population: a. Subjects on 1.5 mg only b. Subjects on 0.75 mg only c. Subjects with any dose modification* * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg
Statistics:	The actual values and change from baseline will be summarized by descriptive statistics (n, missing values, mean, median, SD, SE, minimum, and maximum) by visit. No multiplicity adjustment will be done. The analysis of Mean change in FBG at 24 weeks will use the MMRM. Missing data will be assumed missing at random and will be accommodated by the MMRM. The MMRM using restricted maximum likelihood will be done for analyses (note: statistical comparison will not be conducted) during the entire study period. An unstructured covariance structure will be used to model the within-patient variability and implicitly adjust for missing data. If this analysis fails to converge, the following covariance structures will be tested in order.

1. Toeplitz with heterogeneity
2. Autoregressive with heterogeneity, by visit
3. Compound symmetry with heterogeneous variances, by visit 4. Toeplitz
5. Autoregressive
6. Compound symmetry without heterogeneous variances, by visit

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares mean using Type III sum of squares.

If none of the models converge then an analysis of covariance using LOCF imputation with similar terms as in the MMRM (except no terms that include visit) will be used in its place. The model will evaluate the change from baseline in FBG as the dependent variable and the baseline value of FBG as covariate.

The MMRM for each of the endpoints will include the respective baseline score and any covariate. Baseline HbA1c use and baseline insulin use will be included as covariate in the model if convergence is met. If convergence is not met with baseline insulin level and insulin regimen as covariates, then just insulin use(yes/no) will be used for insulin usage.

Additionally, all the analysis will be repeated for the below mentioned subgroups:

- age (<65 year and ≥65 year)
- HbA1c (<8.5 and ≥8.5)
- Sex (Female and male)
- BMI category (<27 kg/m^2) and ≥ 27 kg/m^2)

Line plot will be plotted to show the trend of FBG lowering. Mean change values will be used by timepoint for plotting.

20.3 Mean change in systolic blood pressure, diastolic blood pressure, and pulse rate from baseline to Week 24

20.3.1 Variables and derivations

Variables:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse (beats per minute)

Derivations:

- Systolic and Diastolic blood pressure, Pulse rate results between visit baseline visit 2 (week 0) and visit 8 (week 24) will be used.

20.3.2 Analyses

Population:	SAF and PP
Stratification:	Table: Add the strata as needed in case subjects with dose modification exceeding 20% based on enrolled population: a. Subjects on 1.5 mg only b. Subjects on 0.75 mg only c. Subjects with any dose modification* * Subjects who have received at least one dose of 1.5 mg and at least one dose of 0.75 mg
Statistics:	The actual values and change from baseline will be summarized by descriptive statistics (n, missing values, mean, median, SD, SE, minimum, and maximum) by visit. No multiplicity adjustment will be done. The analysis of Mean change in Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg) and Pulse (beats per minute) at 24 weeks will use the MMRM. Missing data will be assumed missing at random and will be accommodated by the MMRM. The MMRM using restricted maximum likelihood will be done for analyses (note: statistical comparison will not be conducted)

during the entire study period. An unstructured covariance structure will be used to model the within-patient variability and implicitly adjust for missing data. If this analysis fails to converge, the following covariance structures will be tested in order.

1. Toeplitz with heterogeneity
2. Autoregressive with heterogeneity, by visit
3. Compound symmetry with heterogeneous variances, by visit 4. Toeplitz
5. Autoregressive
6. Compound symmetry without heterogeneous variances, by visit

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares mean using Type III sum of squares.

If none of the models converge then an analysis of covariance using LOCF imputation with similar terms as in the MMRM (except no terms that include visit) will be used in its place. The model will evaluate the change from baseline in SBP, DBP and pulse rate respectively as the dependent variables and the baseline value of SBP, DBP and pulse rate respectively as covariate. Separate model will be run for each parameter.

The MMRM for each of the endpoints will include the respective baseline score and any covariate. Baseline HbA1c and baseline insulin use will be included as covariate in the model if convergence is met. If convergence is not met with baseline insulin level and insulin regimen as covariates, then just insulin use(yes/no) will be used for insulin usage.

Additionally, all the analysis will be repeated for the below mentioned subgroups:

- age (<65 year and ≥65 year)
- HbA1c (<8.5 and ≥8.5)

- Sex (Female and male)
- BMI category (<27 kg/m^2) and ≥ 27 kg/m^2)

21. Other assessments

The listings will be presented for 12-Lead ECG data at screening using SAF population.

The Physical examination assessment will be presented in data listings and summarised as number and percentage (n and %) using SAF population. Physical examination data will be classified as normal and abnormal.

22. Revision history

Version	Date	Change
1.0	19-Dec-2022	Original Document
2.0	19-May-2023	1. Updated Enroll Population Definition 2. Added plots for the HbA1c analysis 3. Updated primary and secondary analysis text for the 95% CI presentation in mock shells. 4. Added plots vital sign parameters.

23. Appendix 1: Programming Conventions for Tables, Data Listings and Figures (TLFs)

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures. Tables, figures, and listings will be produced with validated software. The production environment for statistical analysis consists of statistical analysis software; for example, the SAS System version 9.4 or later.

All percentages (%) for a specific summary are calculated using the total number of subjects included in the relevant analysis population as the denominator, unless otherwise specified.

Data listings will be based on all subjects, unless otherwise specified.

In general, if we have no response or record for respective parameter in data (i.e., n=0) then while presenting statistics in table only n will be presented as “0” and other statistics will be left blank. In case we have only one response or record for respective parameter (i.e., n=1) in data then statistic SD in table will be left blank.

By default, for continuous measures, summary statistics will include, unless otherwise specified:

- n
- Mean
- Median
- Maximum
- Minimum
- Standard error
- SD
- Frequency of Missing Values.

For categorical measures, summary statistics will include, unless otherwise specified:

- Frequency of non-missing values
- Percentage, and
- Frequency of Missing Values.

23.1 Paper Size, Orientation and Margins

The margin, page size and line size specifications as stipulated in Table 23.1 will be used for the presentation of all TLFs.

Table 23.1: Output margin, page size and line size specifications

	Landscape	Portrait
Margins (Inches):		
Top	1.25	1
Bottom	1	1
Left	1	1.25
Right	1	1
Header (Inches)	0.5	0.5
Footer (Inches)	0.5	0.5
SAS® specifications:		
PAGESIZE	46	67
LINE SIZE	134	93
Body Font Size	10	10
Heading font Size	12	12

23.2 Fonts

The font type “Times New Roman” must be used for tables, listings, and figures, with a minimum font size of 9, and it should be consistent for the whole report. The font colour must be black for tables, listings, and figures.

Colours are allowed for figures if the data series can be distinguished clearly if printed on black and white paper.

23.3 Header Information

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page).
- The header should be placed at the top of the page (same place on each page).
- The Sponsor name should appear in row 1, left-aligned in header.

- The word “Interim Analysis/Final Analysis/Protocol-Specified Analysis” would be appeared in row 1, cantered aligned in header.
- The protocol number should appear in row 2, left-aligned in header.
- The word “Cut-off date: DDMMMYYYY” would appear in row 2, centre aligned in header
- The word “CONFIDENTIAL” should appear in row 1, centered aligned at footer in compiled file only.
- The TLF identification number should appear in row 3, centered in header.
- The TLF title should start in row 4, centered in header.
- The TLF population should appear in row 5, centered in header. The population should be spelled out in full, e.g., Enrolled Analysis Set.
- Row 6 in header should be a continuous row of underscores (‘_’) (the number of underscores should equal the line size).
- Row 7 in header should be a blank line.
- Sentence case should be used for titles in header.
- Titles should not contain quotation marks or footnote references.
- The column headings should be underlined with a row of underscores (‘_’).
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- Column headings containing numbers should be centered.
- Column headings should be in mixed case.
- In general, the analysis population count should appear in the column header in the form “(N=XX)”.
- The page identification in the format Page X of Y (where Y is the total number of pages for the TLF) should appear in row 2, right aligned at Footer for compiled TLFs if required.

23.4 Table, Listing and Figure (TLF) Conventions

23.4.1 General

- The first row in the body of the table or data listing should be blank.
- The left-hand column should start in Column 1.
- Rounding should be done with the SAS® function ROUND if applicable.
- Numerical values in tables should be rounded and not truncated as per section (24.4.2) for respective statistics.

- Numerical values should be centre aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The study drug should appear first in tables with treatment group as columns.
- The width of the TLF should match the line size.

23.4.2 Univariate statistics

- Statistics should be presented in the same order across tables (i.e., n, missing values, mean, SD, SE minimum, median and maximum) as appropriate.
- If the original data has N decimal places, then the summary statistics would have the following decimal places:
  - Minimum, maximum: N.
  - Mean and median: N +1.
  - SD: N + 2.
  - Point estimate: N+1.

23.4.3 Frequencies and percentages [m, n (%)]

- Count values should be reported with one space between the left side of the percentage and the right side of the number of events. Percentage should be presented inside brackets or parentheses, and it should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percentage is less than 100.0. An example is given below:
  - 156, 77 (100.0)
  - 56, 50 (64.9)
  - 0 (0.0)
- Percentages of 0 or 100 may be reported to 0 decimal places. Confidence intervals (CIs)
- CIs should be presented with one additional decimal place as that of the raw data.
- CIs will be presented as [lower bound, upper bound].

23.4.4 Ratios/Estimate

- Ratios/estimates should be reported with one additional decimal place as that of the raw data.

23.4.5 Spacing

- There should be a minimum of 1 blank space between columns (preferably 2).

23.4.6 Missing values

- A “0” should be used to indicate a zero frequency.
- A blank should be used to indicate missing data in data listings.

23.5 Table, Listing and Figure output conventions

The compiled file will be presented in PDF format, with TOC for listings and tables/figures separately.

The tables, listings and figures will be provided in RTF and PDF files using the SAS® Output Delivery System (ODS).

All percentages (%) for a specific summary should be calculated using the total number of subjects included in the relevant analysis population as the denominator, unless otherwise specified.

Data listings will be based on all subjects treated, unless otherwise specified.

23.6 Dates and times

In footer of the TLFs, date and time will be presented in format ddmmyyyy and hh: mm. Depending on data available, dates and times will take the form ddmmyyyy and hh: mm.

23.7 Spelling format

The spelling format to be used is English US.

23.8 Presentation of treatment

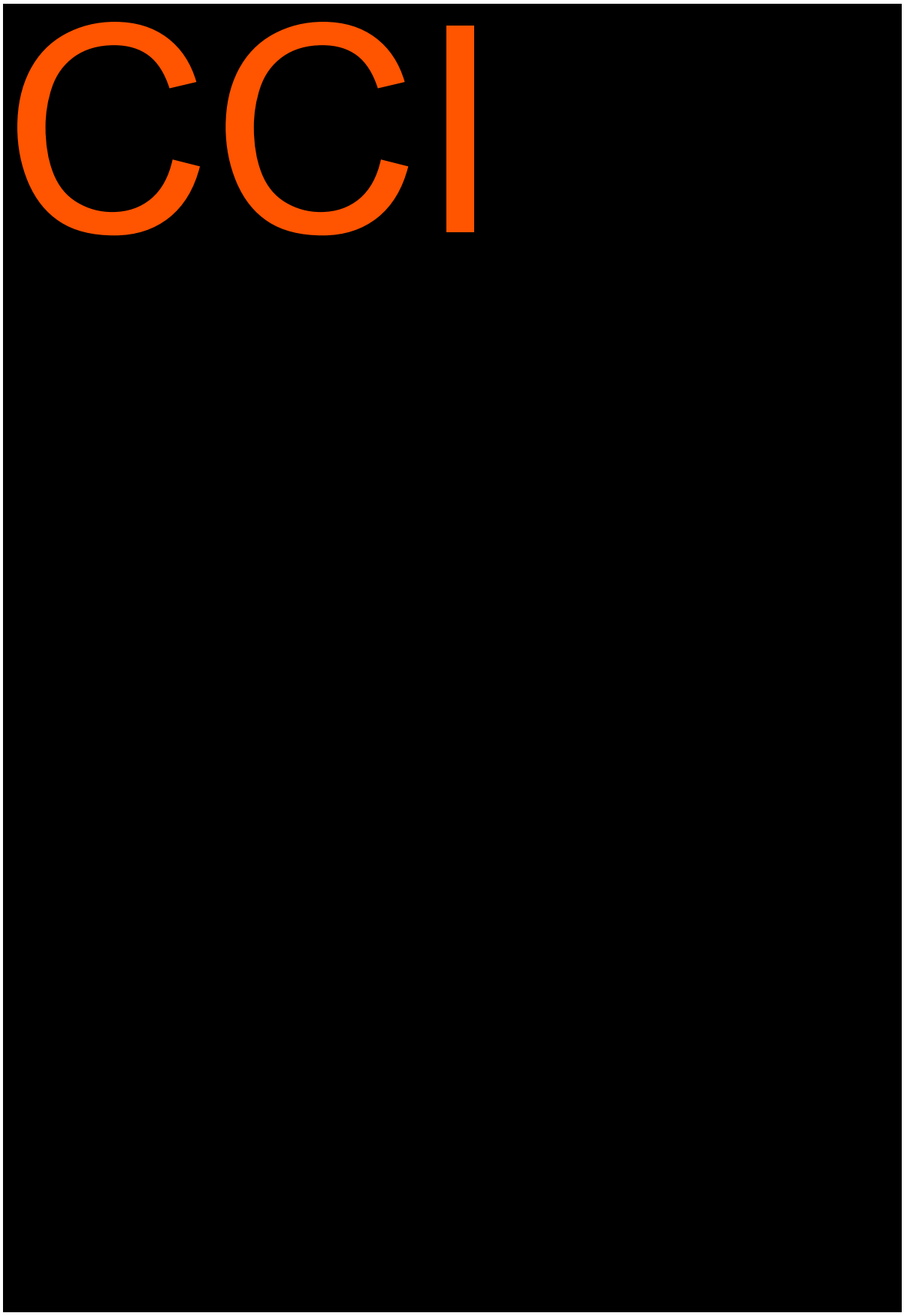
Treatment: Dulaglutide (0.75 or 1.5 mg)

23.9 Presentation of visits

- Visit 1 (Week -2) Screening
- Visit 2 (Week 0)

- Visit 3 (Week 4)
- Visit 4 (Week 8)
- Visit 5 (Week 12)
- Visit 6 (Week 16)
- Visit 7 (Week 20)
- Visit 8 (Week 24)
- Visit 801 (Week 28) Follow up


CCI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