Statistical Analysis Plan H9X-JE-GBGK

A Phase 4 Study to Evaluate Glucodynamic Effects of Dulaglutide in Japanese Patients with Type 2 Diabetes Mellitus

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STATISTICAL ANALYSIS PLAN

A Phase 4 Study to Evaluate Glucodynamic Effects of Dulaglutide in Japanese Patients with Type 2 Diabetes Mellitus

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Study Drug: Dulaglutide (LY2189265)

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
CGM	Continuous glucose monitoring
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
iAUC	Invremental AUC
ICH	International Council on Harmonisation
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
MTT	Meal tolerance test
NA	Not applicable
PD	Pharmacodynamic
QW	Once weekly
SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard Operating Procedure
TBL	Total bilirubin

T2D	Type 2 diabetes mellitus
TFLs	Tables, Figures, and Listings
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 12 July 2017).

This SAP describes the planned analysis of the safety, tolerability and pharmacodynamic (PD) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PD analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be signed off prior to first patient administration for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Eli Lilly and Company and Covance EC Biometrics and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Council on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is

- To evaluate glucodynamic effects of dulaglutide 0.75 mg compared with placebo in area under the glucose concentration versus time curve from 0 to 4 hours (glucose AUC[0-4h]) at 4 weeks in Japanese patients with type 2 diabetes mellitus (T2D).

4.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate PD effects of dulaglutide 0.75 mg compared with placebo at 4 weeks.
- To evaluate safety and tolerability of dulaglutide 0.75 mg for 4 weeks.

4.3 Tertiary/Exploratory Objectives

The exploratory objectives are:

- To evaluate daily glucose variability.
- To evaluate satiety after standardized test meal.

5. STUDY DESIGN

This study is a Phase 4, single-center, randomized, cross-over, single-blind, placebo-controlled study to evaluate glucodynamic effects of dulaglutide after a standardized test meal in Japanese patients with T2D.

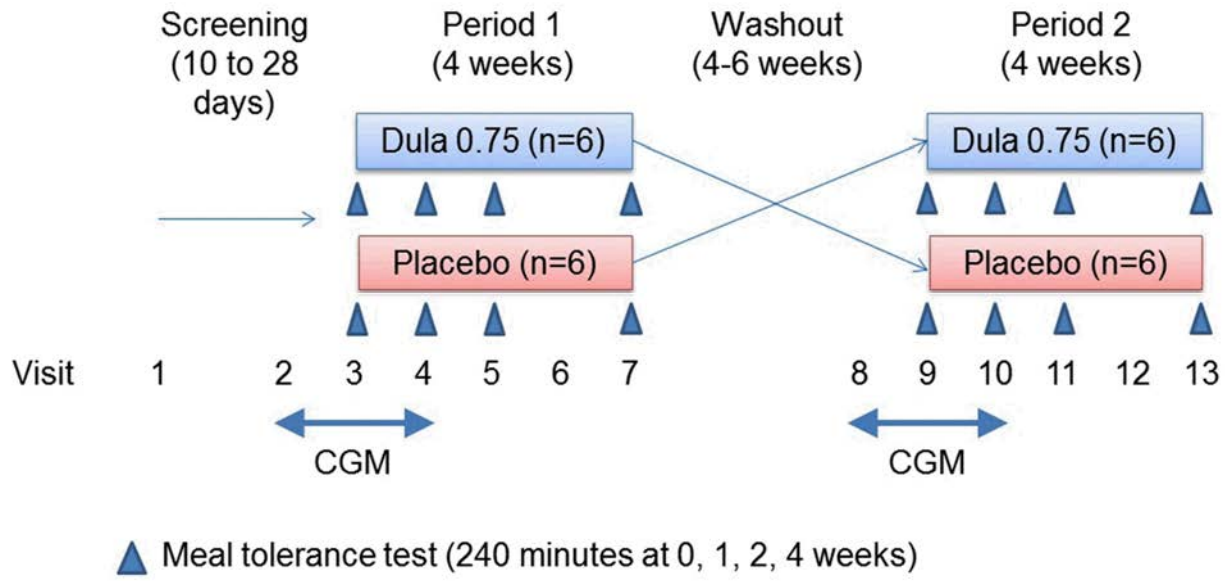
The study includes a 10- to 28-day screening period, a 4-week treatment period (Period 1), a 4- to 6-week washout period, and a 4-week treatment period (Period 2).

Screening tests will be performed at Visit 1. After confirming eligibility, the patient will be randomized in a 1:1 ratio to dulaglutide 0.75 mg or placebo treatment in Period 1.

Meal tolerance test (MTT) will be performed at baseline, 1, 2, and 4 weeks for each period. Time points for blood sampling will be 0, 30, 60, 90, 120, 180, and 240 minutes after the start of standardized test meal. Satiety will be also assessed at 0, 60, 120, 180, and 240 minutes after the start of standardized test meal. After completion of Period 1, all patients must have a 4- to 6-week washout period, and then will start Period 2 on the opposite treatment (patients taking dulaglutide will be switched to placebo and patients taking placebo will be switched to dulaglutide).

This is a single-blind study, and the treatment assignments will be blinded to patients until study completion.

Figure 1 illustrates the study design.



Abbreviations: CGM = continuous glucose monitoring; dula = dulaglutide; n = number of patients.

Figure 1. General Study Design

6. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs.

Study Treatment Name	Treatment order in TFL
Placebo QW	1
0.75 mg dulaglutide QW	2

QW = once weekly

7. SAMPLE SIZE JUSTIFICATION

Up to 14 patients may be entered to randomize 12 patients and complete at least 11 patients. Patients will be randomized in a 1:1 ratio to one of two sequences. Assuming one dropout, the sample size of 11 patients would provide 93% power to demonstrate superiority of dulaglutide to placebo. This computation assumes the true treatment difference in glucose AUC(0-4h) is 190 mg*hr/dL, a common standard deviation of 140 mg*hr/dL, intra-patient correlation of 0.3, and a one-sided significance level of 0.025.

Patients who are randomized but do not complete study treatment may be replaced at the discretion of the investigator and Lilly clinical pharmacologist.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all patients who received at least one dose of study drug (dulaglutide or placebo), and have at least one postdose safety assessment.

The "Pharmacodynamic" population will consist of all patients who received at least one dose of study drug (dulaglutide or placebo), and have evaluable pharmacodynamic data.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when patients are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, min, max and N; for log-normal data the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all patients up to the point of withdrawal, with any patients excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for patients included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual patients' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the timepoint. The individual patient's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.3 or greater.

9.2 Demographics and Patient Disposition

Patient disposition will be listed. The demographic variables age, sex, race, ethnicity, body weight, height, body mass index, duration of diabetes, screening HbA1c and fasting blood glucose will be summarized and listed.

9.3 Pharmacodynamic Assessment

9.3.1 Pharmacodynamic Analysis

The baseline for all PD parameters is defined as the premeal value on Day 1 for the relevant period.

Primary Measure

The primary measure of PD is the change from baseline in glucose AUC(0-4h) at 4 weeks.

Secondary Measures

The following secondary measures of PD will be evaluated:

- The change from baseline in fasting blood glucose at 1, 2, and 4 weeks
- The change from baseline in postprandial blood glucose (30, 60, 90, 120, 180, and 240 minutes) at 1, 2, and 4 weeks
- The change from baseline in glucose AUC(0-4h) at 1 and 2 weeks
- The change from baseline in insulin (30, 60, 90, 120, 180, and 240 minutes) at 1, 2, and 4 weeks
- The change from baseline in insulin AUC(0-4h) at 1, 2, and 4 weeks
- The change from baseline in C-peptide (30, 60, 90, 120, 180, and 240 minutes) at 1, 2, and 4 weeks
- The change from baseline in C-peptide AUC(0-4h) at 1, 2, and 4 weeks
- The change from baseline in glucagon (30, 60, 90, 120, 180, and 240 minutes) at 1, 2, and 4 weeks
- The change from baseline in glucagon AUC(0-4h) at 1, 2, and 4 weeks
- The change from baseline in triglyceride (30, 60, 90, 120, 180, and 240 minutes) at 1, 2, and 4 weeks
- The change from baseline in triglyceride AUC(0-4h) at 1, 2, and 4 weeks

PD AUCs will be calculated for glucose, insulin, glucagon, c-peptide, and triglyceride data following the standardized test meal at Weeks 0, 1, 2, and 4. The AUC(0-4h) will be calculated using the linear-trapezoidal method and actual times. This analysis will be performed for both original data and adjusted data with the predose value at each period, i.e. incremental AUC (iAUC). The parameters AUC(0-1h), AUC(0-2h), and AUC(0-3h) will also be calculated for glucose, insulin, C-peptide, glucagon and triglyceride together with the corresponding iAUCs.

9.3.2 Pharmacodynamic Statistical Methodology

All PD parameters will be listed and summarized by treatment group and week. Individual observed and changes from baseline in glucose, insulin, glucagon, C-peptide, and triglyceride concentrations will be listed and summarized and their mean time profiles will be plotted by treatment group together with changes from baseline.

PD AUCs and iAUCs on Weeks 0, 1, 2, and 4 will be analyzed using a mixed-effects linear model for glucose, insulin, glucagon, C-peptide, and triglyceride . The model will include

treatment, sequence, period, week and treatment-by-week interaction as fixed effects, baseline as a covariate and patient as random effect.

The least squares means and the 95% CIs by treatment group will be tabulated and plotted. Comparisons between dulaglutide and placebo will be performed. Difference of least squares means of dulaglutide to placebo, and the 95% CIs, will be tabulated. Example SAS code is given below:

```
proc mixed data=pd;
class patient treatment sequence period week;
model pd = baseline treatment sequence period week treatment*week / ddfm=kr;
repeated week(treatment) / subject=patient type=un;
lsmeans treatment*week / pdiff alpha=0.05;
run;
```

The repeated patient effect models the within-patient errors using an unstructured variance-covariance matrix. If the analysis fails to converge, the following variance-covariance matrix will be used (in order) until one converges:
1. compound symmetry,
2. banded, and then
3. first-order autoregressive.

Continuous plasma glucose monitoring (CGM)

For the CGM data, parameters will be derived from the raw data collected through Day -1 to Day 6 (7 days), of CGM device use by patient and treatment.

The following notation will be used in the definition:

n represents the number of time points within a day

i represents a time point within a day

m represents a day

Within-day glucose SD:

$$SD_m = \sqrt{\frac{\sum_{i=1}^{n}(BG_i - \left\{\frac{\sum_{i=1}^{n} BG_i}{n}\right\})^2}{n-1}}$$

Mean amplitude of glycemic excursions (MAGE):

this parameter is calculated based on the arithmetic mean of differences between consecutive peaks and nadirs of differences greater than one SD of mean glycemia. Mean of the differences between consecutive peaks and nadirs in BG that meet qualifying criteria

$$MAGE_m = \frac{\sum_{l=1}^{p} |BG_l - BG_{l-h}|}{p}$$

where,

x_l = the low point in consecutive BG time points for the M^{th} day (nadir)

x_{l-h} = the high point in consecutive BG time points for the M^{th} day (peak)

p = the number of qualifying differences: $(BG_l - BG_{l-h}) \geq 1$ SD(daily BG values) and that follow the direction of the first qualifying difference within the BG time points for the M^{th} day

Daily average, daily standard deviation, and daily MAGE from glucose data will be summarized. Individual (by patient) and mean by treatment of glucose data will be plotted over the days.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the patient has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to the first dose. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to the first dose and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of adverse events, the number of patients experiencing an adverse event and the percentage of patients experiencing an adverse event) of treatment-emergent adverse events will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 system organ class and preferred term. The summary and frequency adverse event tables will be presented for all causalities and those considered related to the study drug. Any serious adverse events will be tabulated.

9.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2017 Enhanced Dictionary Version B2 Format). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

eGFR will be calculated as:

$$GFR(male)=194*Scr^{-1.094}*age^{-0.287}$$

$$GFR(female)=GFR(male)*0.739$$

All clinical chemistry, hematology, urinalysis, urine albumin/creatinine ratio (UACR), eGFR, HbA1c and endocrinology data will be listed. Additionally clinical chemistry, hematology, urinalysis, urine albumin/creatinine ratio (UACR), eGFR, HbA1c and endocrinology data outside the reference ranges will be listed.

Values for any clinical chemistry, hematology, urinalysis, urine albumin/creatinine ratio (UACR), eGFR, HbA1c and endocrinology values outside the reference ranges will be flagged on the individual patient data listings.

9.4.4 Vital signs

Where two or more repeat measurements are performed for vital signs, the median of the original and the repeat values will be used in all subsequent calculations. Where only one repeat measurement is performed for vital signs, the repeat value will be used in all subsequent calculations.

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose within each period. Figures of mean vital signs and mean changes from baseline profiles by treatment will be presented by treatment. Furthermore, values for individual patients will be listed.

Changes from baseline (predose) will be calculated for vitals signs.

9.4.5 Satiety after Standardized Test Meal

A visual analogue scale (VAS) test will be performed to measure perception of satiety (full and hungry). Data will be summarized by treatment and listed along with mean plots showing the profiles for fullness and hunger by treatment and time.

9.4.6 Hypoglycemic Episodes

Hypoglycemic episodes will be listed.

9.4.7 Hepatic Monitoring

If a patient experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests will be performed to confirm the abnormality.

If a patient has a liver abnormality then they will be included in the listings and summaries detailed below.

The patients' liver disease history and associated person liver disease history data will be listed. Any concomitant medication of acetaminophen/paracetamol will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and a biopsy assessment will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized in a frequency table by treatment and will also be listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual patient data listings.

9.4.8 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

9.4.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters and appropriate summary statistics will be reported to three significant figures. Observed concentration data should be reported as received. Observed time data should be reported as received. N and percentage values should be reported as whole

numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of patients or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the centre of the table, such as, “No serious adverse events occurred for this study.”