Statistical Analysis Plan

Study Code	D1690L00067
Edition Number	V1.1
Date	08 February 2018

Effects of Dapagliflozin Compared with Glimepiride on Body Composition in Patients with Type 2 Diabetes Inadequately Controlled with Metformin

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Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
A1C	Glycated hemoglobin
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
BP	Blood Pressure
CBC	Complete Blood Count
CK	Creatinine Kinase
CPMP	Committee for Proprietary Medicinal Products (EU)
CRF	Case Report Form
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computerized Tomography
DNA	Deoxyribonucleic Acid
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	DTSQ Change Version
DTSQs	DTSQ Status Version
DXA	Dual Energy Xray Absorptiometry

Abbreviation or special term	**Explanation**
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
FDA	Food and Drug Administration (US)
FFA	Free Fatty Acid
FBG	Fasting Blood Glucose
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDL-C	High-density Lipoprotein Cholesterol
HRT	Hormone replacement Therapy
ICH	International Conference on Harmonisation
IPS	Investigational Products
LDL-C	Low-density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
N.B.	Nota Bene, mind you
OAD	Oral Antidiabetic Drug
pCRF	Paper Case Report Form
PK	Pharmacokinetics
PPG	Postprandial Plasma Glucose
PPG AUC	Postprandial Glucose Area Under the Curve

Abbreviation or special term	**Explanation**
PRO	Patient-reported Outcome
SAE	Serious Adverse Event (see definition in Section6.9).
SAT	Subcutaneous adipose tissue
SDT	Study Delivery Team
SGLT1	Sodium-dependent Glucose Transporter 1
SGLT2	Sodium-dependent Glucose Transporter 2
SU	Sulphonylurea(s)
TG	Triglyceride
TSH	Thyroid-stimulating Hormone
T2DM	Type 2 Diabetes Mellitus
UACR	Urine Albumin:Creatinine Ratio
ULN	Upper Limit of Normal
VAT	Visceral adipose tissue
WBDC	Web Based Data Capture
WOCBP	Women of child bearing potential

AMENDMENT HISTORY

Date	Brief description of change
11Jan2016	N/A First Version
24AUG2017	Sensitivity Analysis are added as supportive analysis to assess the impact on gender ratio on primary and secondary endpoints.

1. STUDY DETAILS

This statistical analysis plan (SAP) provides a detailed description of the statistical methods proposed in the study protocol 08 February 2018 dated on 07JUN2016 version 3.

1.1 Study objectives

The primary objective of the study is to evaluate the effect of Dapagliflozin compared to Glimepiride on body composition in Korean Type 2 Diabetes Mellitus (T2DM) subjects, by assessing the changes in total body fat mass from baseline using DXA scan in 52 weeks after the start of the treatment.

There are multiple secondary objectives in this study;

To evaluate the efficacy in improving glycaemic control of Dapagliflozin compared to Glimepiride in subjects with type 2 diabetes by following assessments:

- The change in HbA1c levels from baseline to 52 weeks (baseline, 12, 24, 36 and 52 weeks)
- The proportion of subjects achieving a glycemic response, defined as HbA1c <7.0% at Week 52
- The change in FBS levels from baseline to 52 weeks (baseline, 4, 12, 24, 36 and 52 weeks)

To evaluate the effect on body weight of Dapagliflozin compared to Glimepiride in subjects with type 2 diabetes, by assessing changes in body weight, waist circumference, BMI from baseline to 4, 12, 24, 36 and 52weeks.

To evaluate the effect on blood pressure of Dapagliflozin compared to Glimepiride in subjects with type 2 diabetes, by assessing changes in SBP and DBP from baseline 4, 12, 24, 36 and 52weeks.

To evaluate the effect on adipose tissue and lean volume of Dapagliflozin compared to Glimepiride in subjects with type 2 diabetes, by assessing changes in abdominal VAT and SAT area, VAT/SAT ratio using abdominal CT from baseline to 52 weeks (baseline, 52 weeks) and changes in lean mass from baseline using Dual Energy X-ray Absorptiometry (DXA) scan to 52 weeks (baseline, 52 weeks).

To evaluate the effect on insulin resistance of Dapagliflozin compared to Glimepiride in subjects with type 2 diabetes, by assessing changes in high-sensitivity CRP (hsCRP) and adiponectin from baseline to 52 weeks (baseline, 52 weeks).

To evaluate the safety of Dapagliflozin and Glimepiride, by following assessments:

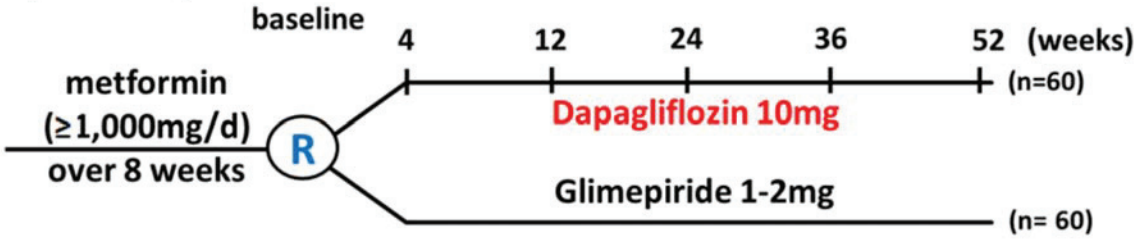
- Changes in CBC, electrolytes, lipid, urinalysis from baseline to 4, 12, 24, 36 and 52weeks

- Number, frequency and proportion of subjects exposed to adverse events
- Number, frequency and proportion of subjects exposed to hypoglycemic events

1.2 Study design

This is a 52 weeks, randomized, open-label, parallel-group, multi-centres phase IV study to evaluate the effects of Dapagliflozin compared with Glimepiride on body composition in patients with Type 2 Diabetes inadequately controlled with Metformin. 120 participants will be randomized 1:1 to receive Dapagliflozin 10 mg qd or Glimepiride 1~2 mg qd in an open-label manner for 12 months as add-on to Metformin 1000 mg. The study design and plan are summarized in Figure 1 below and Table 1 in study protocol.

Figure 1 Study Flow Chart



Scheduled visits of the study include measurements at baseline, 4, 12, 24, 36 and 52 weeks. Subjects with T2DM and inadequate glycaemic control (HbA1c ≥7.5% and ≤ 9.5%) having stable Metformin monotherapy ≥1000 mg/day for at least 8 weeks prior to enrolment will be eligible to enter the study. Subjects early terminate or complete study treatment will not be further followed after End of Treatment (EoT) Visit. Table 1 in study protocol provides a detailed schedule of assessments of events related to the study objective.

1.3 Number of subjects

To evaluate the effect of Dapagliflozin on body composition in Korean T2DM subjects:

Redacted

2. ANALYSIS SETS

2.1 Definition of analysis sets

Patient inclusion in each of the analysis sets will be finalised prior to database lock. For analyses and displays based on Safety Analysis Set (SAF), subjects will be classified according to the actual treatment they received. All other analyses will be performed based on treatment group to which subjects were randomized.

2.1.1 All Patients Enrolled Set [ENR]

The all patients enrolled (ENR) set will include all patients who gave consent to participate in the study.

2.1.2 All Subjects Randomized Set [RND]

The all subjects randomized (RND) set will contain all subjects in the ENR set who were randomized to one of the treatment arms.

2.1.3 Safety Analysis Set [SAF]

The safety analysis set [SAF] will include all RND subjects who received at least one dose of study medication during treatment period.

If there is any doubt whether a subject was treated or not, they will be assumed treated for the purposes of analysis.

For analyses based on SAF, subjects who were dispensed with the wrong treatment (treatment other than the one they are randomized to) will be counted in the treatment group for which they actually received medication.

2.1.4 Full Analysis Set [FAS]

The full analysis set [FAS] will include all RND subjects who received at least one dose of study medication during the 52 week treatment period and have a non-missing baseline value and at least one post-baseline value for primary efficacy variable (total body fat mass).

Whenever using the FAS, subjects will be presented in the treatment group to which they were randomized.

2.1.5 Per-Protocol Set [PPS]

The per-protocol set [PPS] is a subset of the FAS consisting of subjects who do not violate the terms of the protocol, which may affect the efficacy endpoints significantly (relevant protocol deviators).

All decisions to exclude subjects from the FAS set to create the PPS set will be made prior to DB locking.

Whenever using the PPS, subjects will be presented in the treatment group to which they were randomized.

2.2 Violations and deviations

Protocol deviations (PDs) will be identified via programming to complement protocol deviation log. If a patient meets any of the following criteria, the patient will be reviewed and may be considered to be a relevant deviator, and consequently all data for that patient will be excluded from the PPS population. All relevant and irrelevant major/critical protocol deviations will be tabulated and listed and will include, but will not be limited to;

- Patients failing to meet inclusion/exclusion criteria but mistakenly randomized.
- Randomized patients who failed to receive treatment.
- Prohibited concomitant medications.
- Receiving wrong treatment.
- Developing withdrawal criteria whilst on the study but are not withdrawn;

Patients with poor treatment compliance are defined as those taking < 80% or > 120% of planned Investigating Product (IP). Treatment compliance algorithm will be discussed in a separate section.

A list of prohibited concomitant medications is provided in the study protocol, Section 6.15.2. Correspond drug names is listed in the Appendix 1 of the SAP.

If a patient satisfies more than one of the reasons for protocol deviation listed above, and is judged to have both relevant and irrelevant deviations, then s/he will be defined as a relevant deviator. For tabulation purposes s/he will be counted as a relevant deviator once overall, but also once within each deviation reason.

As drug dispense/return/lost information is not captured on CRF, calculated poor compliance defined above will be programmed to compare with poor treatment compliance reported in the PD log.

3. A LIST OF MINOR PROTOCOL DEVIATIONS WILL ALSO BE PROVIDED. ANALYSIS METHODS

Statistical summaries will be performed by QuintilesIMS using SAS version 9.2 (or higher) and where appropriate, additional validated software.

3.1 General Principles

All safety outcome summaries will be performed on the SAF whilst all efficacy analyses will be performed on FAS or PPS (PPS for sensitivity analyses of efficacy endpoints) unless otherwise stated. In addition to the formal presentation of results detailed in the following sections, all study data will be listed by centre, patient number and treatment group.

For continuous data, descriptive statistics will be presented for each treatment group and overall, which includes number of patients (n), mean, SD, median, maximum and minimum unless otherwise specified.

For categorical data, the frequency and percentage of patients in each category will be presented. Counts that are zero will be displayed as "0" and all percentages will be based on population size of each treatment group unless otherwise specified.

Data will be listed to the same accuracy as recorded in the eCRF. Mean and median summary statistics will be presented to one additional decimal place, whilst the standard deviation (SD) will be presented to two additional decimal places. Minimum and maximum values will be presented to the same accuracy as recorded on the eCRF.

The default significant level of statistical testing will be 5%; confidence intervals will be two-sided 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

3.1.1 Baseline and Change from Baseline

For all assessments recorded in this study, baseline is defined as the last non-missing value prior to the first dose of study medication (scheduled or unscheduled).

Any assessments taken on the same day of first dose will be deemed to have been collected pre-dose and therefore eligible to be selected as the baseline value. If measurement from Visit 2 is missing, Visit 1 or other unscheduled visit will be used.

Change from baseline will be calculated as difference between the values measured at a specific time point after baseline minus baseline value.

3.1.2 Reference Start Date and Study Day

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first administration of trial medication, (Day 1 is the day of the first injection of trial medication), or for subjects randomized but not treated it is the day of randomization, and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference date then:

- Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date then:

- Study Day = (date of event – reference date).

If the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be calculated based on the available level of data. For instance, if day part of one calculation element is unknown, then the calculation will be carried out on month level (using the conversion of 30.4375 days/month).

3.1.3 Retests, Unscheduled Visits, Early Termination Data and Rescue Visit

In the case of a retest, a visit-specific unscheduled assessment will be created. The latest available measurement within the protocol specified +/- 7 days visit window will be used for by-visit summaries.

Unscheduled measurements (unless assigned to a planned visit number as described in the paragraph above) will not be included in by-visit table summaries and by-visit graphs, but will contribute to the last observation carried forward (LOCF) values described in SAP Section 3.1.4 and also contribute to baseline selection as described in Section 3.1.1.

Subjects who prematurely discontinue the study treatment will complete the same assessments as Visit 7 (End of Treatment Visit), and will not be further followed. Early termination data will be summarized and presented together with End of Treatment (EoT) Visit.

Randomized subjects with a central laboratory Fasting Blood Glucose (FBG) and HbA1c value meeting the criteria for lack of glycaemic control during treatment period may be eligible to receive open-label, prescribed rescue medication which may allow the subject to remain in the trial. Randomized subjects who meet the repeated rescue criteria should be scheduled for a rescue visit. Similar to unscheduled measurements, rescue visit results will not be included in by-visit table summaries but will contribute to LOCF algorithm.

Listings will include all scheduled, unscheduled, rescue visit, retest and early discontinuation data collected in the CRF without any unscheduled visit window mapping to scheduled visits.

3.1.4 Missing Data

LOCF will be used for imputation of missing values of glycaemic control status (HbA1c <7.0%).

Last observation will be carried forward as many times as needed. All available data, including unscheduled visits and rescue visits, will be taken into account when identifying the last observation to be carried forward.

3.1.5 Multicenter Study

Study will include data from approximately 17 sites in Korea, all data will be pooled before analysis.

3.1.6 Multiple Comparisons/ Multiplicity

The statistical significance levels will not be adjusted for multiple hypothesis testing. Consequently, all statistical tests performed with secondary/sensitivity analysis will be interpreted only descriptively.

3.2 Disposition and withdrawals

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

The following subject disposition and withdrawal events will be presented for the ENR set:

- Informed consent signed (ENR)
- Screen failures
- Passed screening but not randomized
- Randomized (RND)
- Randomized but not treated
- Treated, Safety Analysis Set (SAF)
- Full Analysis Set (FAS)
- Per Protocol Analysis Set (PPS)
- Prematurely discontinued from treatment/study
    - Primary reason for premature discontinuation
- Completed treatment/study.

Subjects violating each inclusion and exclusion criteria will only be listed for the ENR set.

3.3 Demographics and Other Baseline Characteristics

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic characteristics will be presented for SAF:

- Age (years) - Calculated relative to date of ICF
- Gender
    - Male
    - Female

        - Post-menopausal
        - Non-menopausal
            - Pregnancy test positive
            - Pregnancy test negative
            - Pregnancy test not performed
- Ethnicity
    - Korean
    - Other
- Subject Experienced Type 1 Diabetes
    - Active
    - Cured
- Time since Type 2 Diabetes diagnosis (years) - Calculated relative to date of ICF

The following baseline characteristics will be presented for FAS:

- Baseline total body fat mass (g)
- Baseline total body lean mass (g)
- Baseline total body fat percentage (%)
- Baseline HbA1c level (%)
- Baseline fasting blood glucose level (mg/dL)
- Baseline body weight (kg)
- Baseline waist circumference (cm)
- Baseline BMI (kg/m^2)
- Baseline SBP (mmHg)
- Baseline DBP (mmHg)
- Baseline VAT/SAT ratio
- VAT and SAT area
- Baseline hsCRP (mg/L)
- Baseline Adiponection (ng/mL)

Definition of baseline is discussed in SAP Section 3.1.1.

3.3.1 Derivations

- Age (Years) will be calculated relative to the date of informed consent:

  - Age (Years) = (Date of Informed Consent Signed – Date of Birth + 1)/365.25
- Time since Type 2 Diabetes diagnosis (years) = (Date of Informed Consent Signed – Date of first diagnosis of Type 2 Diabetes + 1)/365.25
- BMI (kg/m^2) = Weight (kg)/ $Height^2$ (m^2)

3.4 Surgical History, Medical History and Concomitant Procedures

Surgical and medical history will be collected on CRF page "pMH" whilst concomitant procedures will be collected on CRF page "pCP". Captured data will be presented for SAF population.

Collected records will be coded using MedDRA version 20.0 or higher. All coded terms will be summarized by SOC and PT. Subject having multiple records in one category will be counted only once. Records will be presented in alphabetical order.

Additionally, for concomitant procedures, reasons for procedure will be summarized and rescue procedures will be presented additionally.

3.5 Medications

Medications will be captured on CRF page "pCM".

"Prior" medications are medications which stopped prior to the first dose of study medication. All other medications will be considered concomitant. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; concomitant.

All concomitant medications, including rescue medications, will be summarized for SAF set.

All concomitant medications will be coded using AZ Drug Dictionary (AZDD) Version 15.2 to identify their Anatomical Therapeutic Chemical (ATC) classification code and generic term. Multiple drug usage by a patient will be counted only once for each therapeutic class. Records will be presented in alphabetical order.

Rescue medication will be summarized additionally.

3.6 Study Treatment Exposure and Compliance

The investigational product, Dapagliflozin or Glimepiride, and additional drug, Metformin 1000 mg will be taken orally.

Based on randomization results, subject will receive either **Global Retention and Disposal Standard**

- Dapagliflozin tablets, 10 mg, administered orally, once daily as add-on to Metformin 1000 mg; or

- Glimepiride tablets, 1 mg, administered orally 1 or 2 tablets as add-on to Metformin 1000 mg. Glimepiride administration can be up-titrated 1 to 2 mg/day. Glimepiride dose can be down-titrated to a non-zero level at any time to prevent hypoglycemia.

Based on drug administration records, treatment compliance will be calculated for each subject. A subject will be considered compliant if more than 80% and less than 120% (both ends inclusive) of the planned study medication has been taken during the study phase.

Relevant information is captured in CRF page "pDARD", "pDARG", "pDARM" and "pDAROVR".

For SAF set, following statistics will be presented and listed for each subject:

- Actual duration of exposure (days)
- Duration of interruptions (days)
- Cumulative dose (mg)
- Actual dose intensity (mg/day)
- Total planned dose (mg), for subjects receiving Glimepiride only
- Compliance (%)
- Compliance category
- Incidence of study medication overdose
- Incidence of dose adjustment
- Type of dose adjustment
- Reasons for dose adjustment
- Number of dose adjustments per subject

Note that dose adjustment only refers to actual dosage change. Adjustment in prescribed amount of Glimepiride which does not lead to actual dose change will not be considered a dose adjustment.

For Metformin exposure status, only following summaries will be presented:

- Actual duration of exposure (days)
- Duration of interruptions (days)
- Cumulative dose (mg)
- Actual dose intensity (mg/day)

3.6.1 Derivations

- Actual duration of exposure (days) = stop date of administration – start date of administration +1

- Duration of interruptions (days) = Sum of (stop date of each interruption – start date of each interruption +1)
    - For Metformin, if Metformin consumption stops before study medication, duration between Metformin termination and end of study treatment will be considered Metformin interruption.
- Actual dose intensity (mg/day) = Cumulative dose (mg) / Actual duration of exposure (days)
- Total planned dose (mg) of subjects receiving Glimepiride = $\sum_{all\ i}(prescribed\ dose\ level\ at\ period\ i) \times (stop\ date\ of\ period\ i - start\ date\ of\ period\ i)$,

  Where each period refers to a time frame whose prescribed dose level is constant. Whenever the prescribed dose level is changed, a new period shall be created.
- Total Planned dose (mg) of subjects receiving Dapagliflozin = 10 mg/day × Actual duration of exposure (day).
- Compliance is based cumulative dose and the total planned dose, and will be calculated as follows:

$$\text{Compliance (\%)} = 100\% \times \frac{\text{Cumulative Dose}}{\text{Total Planned Dose}}$$

- Compliance will be further categorized into 3 levels:
    - <80%
    - ≥80% and ≤120%
    - >120%

3.7 Primary Efficacy Analysis

3.7.1 Primary Efficacy Variable

The primary efficacy variable of the study is the change in total body fat mass (in grams and percentages) from baseline using DXA scan in 52 weeks after the start of the treatment, which is defined as the total body fat mass at Week 52 subtracts total body fat mass at baseline.

Total body fat mass and percentages will be captured on CRF page “pDXA1” and “pDXA”.

3.7.2 Primary Analysis of Primary Endpoint

The test for equivalence between two treatment groups will be performed for FAS population.

The hypothesis to be tested are given as:

$$H_0: \mu_T = \mu_c \ \ Versus \ \ H_A: \mu_T \neq \mu_C$$

Where μ_T denotes the mean change in test results from Baseline to Week 52 of subjects who received Dapagliflozin (Treatment under investigation, T) and μ_c denotes the mean change in test results from Baseline to Week 52 of subjects who received Glimepiride (Comparator, C).

The primary efficacy variable will be analysed using an ANCOVA model with treatment group as factor and Baseline test results as a covariate, as following:

$$E(Y_{ij}) = \mu_{..} + Trt_i + BaselineY_{ij}$$

Where i=1, 2; j=1, 2,…, n_i.

$E(Y_{ij})$ denotes the mean change in total body fat mass (in g)/percentages from baseline to week 52 of j^{th} subject in treatment group i.

$\mu_{..}$ denotes the overall mean total body mass from baseline to week 52.

Trt_i denotes the treatment effect of each group from the overall mean.

$BaselineY_{ij}$ denotes the baseline total body fat mass of j^{th} subject in treatment group i.

The model will be used to derive a least squares estimate of the treatment difference with corresponding two-sided 95% confidence interval (CI) and two-sided Wald p-value.

Further, two-sided 95% CIs for the primary endpoint within each treatment group will be calculated. Model diagnosis statistics will be presented.

Following SAS code can be used to obtain above statistics:

```
proc glm data=DD;
class TRTP;
model ChgFat=TRTP BaseFat /solution;
lsmeans TRTP/Pdiff=CONTROL('Comparator')cl;
run; quit;
```

In order to descriptively present the primary endpoint, total body fat mass in grams and total percent of body fat from baseline and Week 52 will be presented for FAS set and listed for SAF set. Change from baseline to Week 52 for FAS subjects will also be summarized.

3.7.3 Sensitivity Analysis of Primary Endpoint

To evaluate the impact of protocol compliance on primary efficacy endpoint, primary efficacy analysis method will be repeated on the PPS population.

To evaluate the impact of base-weight in total body fat mass, primary efficacy analysis will be repeated based on total body fat percentage (%) for both FAS and PPS.

To evaluate the impact of gender ratio on primary efficacy endpoint, primary efficacy analysis method will be performed using ANCOVA model with treatment group as factor and Baseline test results and gender as a covariate on FAS and PP population, as following.

$$E(Y_{ij}) = \mu_{..} + Trt_i + BaselineY_{ij} + GenderZij$$

Where i=1, 2; j=1, 2,…, n_i.

$E(Y_{ij})$ denotes the mean change in total body fat mass (in g or %) from baseline to week 52 of j^{th} subject in treatment group i.

$\mu_{..}$ denotes the overall mean total body mass (in g or %) from baseline to week 52.

Trt_i denotes the treatment effect of each group from the overall mean.

$BaselineY_{ij}$ denotes the baseline total body fat mass of j^{th} subject in treatment group i.

$GenderZij$ denotes the gender of j^{th} subject in treatment group i.

The model will be used to derive a least squares estimate of the treatment difference with corresponding two-sided 95% confidence interval (CI) and two-sided Wald p-value.

Further, two-sided 95% CIs for the primary endpoint within each treatment group will be calculated. Model diagnosis statistics will be presented.

Following SAS code can be used to obtain above statistics:

```
proc glm data=DD;
class TRTP gender;
model ChgFat=TRTP BaseFat gender/solution;
lsmeans TRTP/Pdiff=CONTROL('Comparator')cl;
run; quit;
```

3.8 Secondary Efficacy Analyses

The secondary efficacy analyses will be performed for the FAS only. For each variable, the test for equivalence between two treatment groups will be carried out with the following specified statistical methods.

3.8.1 Secondary Efficacy Variables

There are multiple secondary efficacy variables of interest, as following:

The change in HbA1c levels from baseline to 52 weeks, which is defined as the HbA1c level measured at Week 52 (12, 24, 36 and 52 weeks) subtracts the subject's baseline value.

The proportion of subjects achieving a glycemic response, defined as HbA1c <7.0% at Week 52.

The change in FBS levels from baseline to 52 weeks, which is defined as the FBS level measured at Week 52 (4, 12, 24, 36 and 52 weeks) subtract the subject's baseline value.

The changes in body weight, waist circumference, BMI from baseline to 52 (4, 12, 24, 36 and 52) weeks, which is defined as the corresponding results measured at Week 52 (4, 12, 24, 36 and 52) subtract the subject's baseline value.

The changes in SBP and DBP from baseline to 52 (4, 12, 24, 36 and 52 weeks), which is defined as the results measured at Week 52 (4, 12, 24, 36 and 52 weeks) subtract the subject's baseline value.

The changes in abdominal VAT and SAT area, VAT/SAT ratio using abdominal CT from baseline to 52 weeks, which is defined as the results measured at Week 52 subtract the subject's baseline value.

The changes in lean mass using Dual Energy X-ray Absorptiometry (DXA) from baseline to 52 weeks, which is defined as the results measured at Week 52 subtract the subject's baseline value.

The changes in high-sensitivity CRP (hsCRP) and adiponectin from baseline to 52 weeks, which is defined as the results measured at Week 52 subtract the subject's baseline value.

3.8.2 Primary Analysis of Secondary Endpoints

To evaluate the difference between two treatment groups regarding change in HbA1c levels from baseline to 52 weeks (12, 24, 36 and 52 weeks), the following hypothesis will be tested:

$$H_0: \mu_T = \mu_c \ Versus \ H_A: \mu_T \neq \mu_C$$

Where μ_T denotes the mean change in test results from Baseline to Week 52 of subjects received Dapagliflozin (Treatment under investigation, T) and μ_c denotes the mean change in test results from Baseline to Week 52 (12, 24, 36 and 52 weeks) of subjects received Glimepiride (Comparator, C).

The secondary variable will be analysed using a Mixed effect Model Repeat Measurement (MMRM) model with treatment group, visit, visit*treatment group and baseline measurement as factors, as following:

$$E(Y_{ijk}) = \beta_0 + \beta_1 Trt_i + \beta_2 V_j + \beta_3 Trt_i \times V_j + \beta_4 Base_{ik}$$

Where i=1, 2; j=1,2,…,5; k=1, 2,…, n_i.

$E(Y_{ijk})$ denotes the change in test result from baseline to the j^{th} visit post-baseline of the k^{th} subject in treatment group i.

Trt_i denotes the treatment effect of each group.

V_j denotes the j^{th} visit post-baseline.

$Trt_i \times V_j$ denotes the interaction term of treatment group and visit.

$Base_{ik}$ denotes the baseline test result of k^{th} subject in treatment group i.

The above model will be applied to analyse the secondary efficacy endpoints. All non-missing visit data will be used. The model will be used to derive a least squares estimate of the treatment difference with a 95% CI and corresponding Wald two-sided p-value. Missing data will not be imputed.

The following SAS code can be used to obtain the above statistics:

```
proc mixed data=DATA; where AVISITN in (X,X,X,X) and
PARAMCD="XXX";
class TRTP AVISIT USUBJID;
model AVAL=TRTP | AVISIT  Base/solution;
repeated AVISIT/type=un subject=usubjid r rcorr;
lsmeans TRTP*AVISIT/diff=CONTROL('Comparator' 'Week52') cl;
```

```
run;
```

In order to descriptively present the HbA1c data, measurement results from baseline and each scheduled post-baseline visit will be presented for FAS set. Results will be listed for SAF set. Change from baseline for FAS subjects will also be summarized for all scheduled post-baseline visits.

To evaluate the proportion of subjects achieving a glycemic response, defined as HbA1c <7.0% at Week 52, following hypothesis will be tested:

$$H_0: \pi_T = \pi_c \ \ Versus \ \ H_A: \pi_T \neq \pi_C$$

In this secondary analysis, the successful event is to achieve an HbA1c<7.0 at Week 52. In above hypothesis, π_T denotes the probability of success for subjects received Dapagliflozin (Treatment under investigation, T) and π_C denotes the probability of success for subjects received Glimepiride (Comparator, C). To obtain a complete data structure, missing data will be imputed using LOCF.

The secondary variable will be analysed using a Logistic Regression model with treatment group and baseline measurement as factor, as following:

$$Logit(E(P_{ij})) = \beta_0 + \beta_1 Trt_i + \beta_2 Base_{ij}$$

Where i=1, 2; j=1, 2,…, n_i.

$Logit(E(P_{ij}))$ denotes the logit (log-odds) of the expected probability of success at Week 52 for the j^{th} subject in treatment group i.

Trt_i denotes the treatment effect of each group.

$Base_{ij}$ denotes the baseline numeric test result (in this case, baseline HbA1c level) of j^{th} subject in treatment group i.

Above model will be applied to analyse the secondary efficacy endpoint. The model will be used to derive an estimated odds ratio between two treatment groups (treatment versus comparator) together with a 95% confidence interval and corresponding Wald two-sided p-value.

Following SAS code can be used to obtain above statistics:

```
proc logistic data=Data descending;
class AVALC(ref='N') TRTP (ref='Comparator')/param=glm;
model AVALC (ref='N')= TRTP Base/link=logit;
lsmeans TRTP/e diff=CONTROL('Comparator') cl oddsratio;
run;
```

In order to descriptively present the HbA1c classes, measurement results (proportion of subjects having HbA1c<7.0) from baseline will be presented for FAS set. Results will be listed for SAF set.

To evaluate the change in FBS levels from baseline to 52 weeks (4, 12, 24, 36 and 52 weeks), which is defined as the FBS level measured at Week 52 (4, 12, 24, 36 and 52 weeks) subtract the subject's baseline value.

The statistical modelling and analysis will be performed in the same manner as secondary efficacy variable HbA1c level using a MMRM model.

In order to descriptively present the FBS levels, measurement results from baseline and each scheduled post-baseline visit will be presented for FAS set. Results will be listed for SAF set. Change from baseline for FAS subjects will also be summarized for all scheduled post-baseline visits.

To evaluate the changes in body weight, waist circumference, BMI from baseline to 52 weeks (4, 12, 24, 36 and 52), which is defined as the corresponding results measured at Week 52 (4, 12, 24, 36 and 52) subtract the subject's baseline value.

The statistical modelling and analysis will be performed in the same manner as secondary efficacy variable HbA1c level using a MMRM model.

Descriptive presentation of body weight, waist circumference and BMI will be prepared together with other vital signs in FAS set.

To evaluate the changes in SBP and DBP from baseline to 52 (4, 12, 24, 36 and 52 weeks), which is defined as the results measured at Week 52 (4, 12, 24, 36 and 52 weeks) subtract the subject's baseline value.

The statistical modelling and analysis will be performed in the same manner as secondary efficacy variable HbA1c level using a MMRM model.

Descriptive presentation of blood pressure will be prepared for FAS set, and together with other vital signs in SAF set. Results will be listed for SAF set.

To evaluate the changes in abdominal VAT and SAT area, VAT/SAT ratio using abdominal CT from baseline to 52 weeks, which is defined as the results measured at Week 52 subtract the subject's baseline value.

The statistical modelling and analysis will be performed in the same manner as the primary efficacy variable using an ANCOVA model.

In order to descriptively present the VAT and SAT levels, measurement results (VAT, SAT and VAT/SAT ratio) from baseline and Week 52 will be presented for FAS set. Results will be listed for SAF set. Change from baseline to Week 52 for FAS subjects will also be summarized.

To evaluate the changes in lean mass using Dual Energy X-ray Absorptiometry (DXA) from baseline to 52 weeks, which is defined as the results measured at Week 52 subtract the subject's baseline value.

The statistical modelling and analysis will be performed in the same manner as the primary efficacy variable using an ANCOVA model.

In order to descriptively present the lean mass from baseline and Week 52 will be presented for FAS set. Results will be listed for SAF set. Change from baseline to Week 52 for FAS subjects will also be summarized.

To evaluate the changes in high-sensitivity CRP (hsCRP) and adiponectin from baseline to 52 weeks, which is defined as the results measured at Week 52 subtract the subject's baseline value.

The statistical modelling and analysis will be performed in the same manner as the primary efficacy variable using an ANCOVA model.

In order to descriptively present the hsCRP and adiponectin levels, measurement results from baseline and Week 52 will be presented for FAS set. Results will be listed for SAF set. Change from baseline to Week 52 for FAS subjects will also be summarized.

3.8.3 Sensitivity Analysis of Secondary Endpoints

To assess the robustness of the missing data imputation (LOCF), the same model and statistics will be generated for FAS population with only truly observed data when evaluating proportion of subjects achieving a glycemic response.

To evaluate the impact of protocol compliance on secondary efficacy endpoint, secondary efficacy models (with imputed data for glycemic response) method will be repeated on the PPS population.

To evaluate the impact of gender ratio on secondary efficacy endpoints, the secondary endpoints will be analyzed as a sensitivity analysis by a mixed model for repeated measures (MMRM) where all post-baseline secondary endpoints (HbA1c levels, FBS levels, body weight, waist circumference, BMI, SBP and DBP) obtained at all planned visits before discontinuation from randomized treatment and visit and treatment are included as fixed factors and Baseline secondary endpoints and gender as covariates. Furthermore, interaction terms of visit by treatment, visit by gender and visit by respective Baseline secondary

endpoints will be included. An unstructured covariance matrix for respective Baseline secondary endpoint measurements within same patient will be employed. Regarding missing data this analysis approach relies on the assumption that data are missing at random. The estimated differences between each treatment groups at Week 52 and corresponding two sided p-values and 95% CI will be presented.

To evaluate the impact of gender ratio on secondary efficacy endpoint VAT/SAT area, VAT/SAT ratio and total body lean mass, these parameters will be analysed using ANCOVA model with treatment group as factor and Baseline test results and gender as a covariate on FAS and PPS population. The statistical modelling and analysis will be performed in the same manner as the primary efficacy variable using an ANCOVA model (Sensitivity Analysis).

3.9 Safety Analyses

All safety analyses will be performed based on SAF set. There will be no statistical comparison between treatment groups for safety data except hypoglycemic events.

All sub-sections below will be listed for SAF set.

3.9.1 Adverse Events (AEs)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

AEs will be collected on CRF form “pAE” from the first dosing day to EOT visit, and all recorded AEs will be reported in tables and listings.

Adverse Events (AEs) will be coded using the MedDRA central coding dictionary, Version 20.0. The terms not yet coded in the data management transfer will be summarized in the ‘Uncoded’ category.

Pre-existing conditions will be recorded at baseline on Medical History page of CRF. If a pre-existing condition changes in severity, it will be reported as an AE. If a persistent AE becomes more severe, it should be recorded again with the updated severity.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the output templates. The focus of adverse event reporting in result tables will be based on Treatment Emergent Adverse Events (TEAEs).

Incidence of AEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down by maximum intensity and relationship to study medication. In the case that a patient reports multiple AEs within the same category, the AE with worst severity and strongest relationship will be used in the corresponding summaries.

3.9.1.1 Intensity

The patient (parents/legal guardians) will be asked to assess the maximum intensity of the reported AEs according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities).

An AE with missing severity grade will be considered as Moderate.

3.9.1.2 Relationship to Study Treatment

The investigator will assess causal relationship between Investigational Product (IP, which does not include Metformin) and each AE, and answer 'yes' or 'no' to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?".

An AE with missing causal relationship will be considered related.

3.9.1.3 AEs Leading to Study Withdrawal/ Treatment Discontinuation

AEs leading to study withdrawal and permanent discontinuation of study medication are AE records where "Study drug permanently discontinued due to this adverse event" is captured on "pAE" CRF page as the action taken with study medication. Since in this study, end of treatment is equivalent to end of study, they information can also be extracted from question "Does this AE cause patient's withdrawal from study" on "pAE" CRF.

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

3.9.1.4 AEs Leading to Dose Adjustment or Interruption

AEs leading to dose adjustment or interruption are AE records where "Study drug dosage adjusted/temporarily interrupted" is captured on "pAE" CRF page as the action taken with study medication.

For AEs leading to dose adjustment or interruption, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

3.9.1.5 Serious AEs (SAEs)

Serious adverse events (SAEs) are those events recorded as "Serious" on the "pAE" page of the CRF. A summary of serious AEs by SOC and PT will be prepared.

Criteria for SAEs can be found in protocol Section 6.2.

3.9.1.6 AEs Leading to Death

AEs leading to death are those events with an outcome of "fatal", on the "pAE" CRF page. A summary of AEs leading to death by SOC and PT will be prepared.

3.9.1.7 Hypoglycemic Events and Hypoglycemic AEs

Hypoglycemic AEs are captured on "pAE" page of the CRF, and identified using question "Is the Adverse Event a hypoglycemic event?". Hypoglycemic AEs will be presented by SOC and PT.

Subjects reporting at least one episode of a hypoglycemic event, which is not necessarily an AE, and event frequency are collected on CRF page "pDIARYYN2". Summary of incidence rates (event amount and percentages) will be prepared and corresponding 95% Clopper-Pearson exact confidence intervals (for the probability of a subject reporting at least 1 event) will be reported. A comparison between the treatment groups will be performed using two-sided Fisher's exact test and resulting p-value will be reported.

$$H_0: \pi_T = \pi_c \ \ Versus \ \ H_A: \pi_T \neq \pi_C$$

Where π_T denotes the probability of reporting a hypoglycemic event for subjects received Dapagliflozin (Treatment under investigation, T) and π_C denotes the probability of reporting a hypoglycemic event for subjects received Glimepiride (Comparator, C).

Frequencies of hypoglycemic events reported by each subject will be summarized and listed for SAF set.

3.9.2 Deaths

If any patient dies during the study, relevant information will be captured on CRF page "pAE" as a SAE.

Incidences and percentages of death and will be summarized and listed.

3.9.3 Laboratory Evaluations

Results from the central laboratory will be included in the reporting for serum chemistry, hematology and urinalysis. A list of tests to be performed is included in Protocol section 5.2.1.

The following summaries will be provided for laboratory data:

- Actual value of each scheduled visit and change from baseline for each post-baseline scheduled measurement by visit (for quantitative measurements only).
- Incidence of abnormal values according to normal range criteria. Abnormalities will be classified to "Low" if smaller than the lower limit while "High" if larger than the upper limit.
- Shift from baseline according to abnormality status (Low, Normal and High) for each post-baseline scheduled measurement. For urinalysis, shift between normal and abnormal will be prepared.
- Listing of observed results for all laboratory values will be provided with abnormality status flagged.

- Additionally, Change from screening (visit 1) to each post-treatment time point will be reported for CBC, electrolytes, lipid parameters.

3.9.4 ECG Evaluations

ECG results will be captured on CRF page "pECG" and will contain overall assessment based on Investigator's judgment:

- Normal
- Abnormal, Not Clinically Significant (ANCS)
- Abnormal, Clinically Significant (ACS)

For baseline and each post-baseline measurement, the numbers and percentages of patients in each category above will be summarized.

In addition, heart rate, PR interval, QRS interval and QT interval will be summarized and listed for SAF set.

3.9.5 Vital Signs

Vital signs results are recorded on CRF page "pPE1" and "pPE2". The following Vital Signs measurements will be reported for this study:

- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Sitting Pulse Rate (bpm)
- Respiratory Rate (per min)
- Weight (kg)
- BMI (kg/m^2)
- Waist Circumference (cm)
- Baseline Height (cm)

Above vital sign values and change from baseline (applicable to all post-baseline measurements) will be summarized by each scheduled time-point and presented for SAF set. Additionally, Change from screening (visit 1) to each post-treatment time point will be reported for vital signs (pulse).

All observed vital signs will be listed.

3.9.6 Physical Examinations

A physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, head and neck (including head, ears, eyes, nose and throat).

Findings in each body system tested will be summarized for all scheduled visits. The examination at visit 1 will be considered as baseline and change from baseline will be calculated for the following visits.

All physical examination results will be listed for SAF set.

4. CHANGES OF ANALYSIS FROM PROTOCOL

Not Applicable.

5. REFERENCES

D1690L00067 Protocol Version 3 dated 07Jun2016.

Study annotated CRF Version 3.0, dated 22Jul2016.

APPENDIX 1 LIST OF PROHIBITED MEDICATIONS

Prohibited Medication Class	**Generic Term**
Antihyperglycaemic medications	Tolbutamide, Chlorpropamide, Tolazamide, Gliclazide, Glipizide, Glyburide, Nateglinide, Repaglinide, other metformin except IP, Rosiglitazone, Pioglitazone, Acarbose, Voglibose, Vildagliptin, Saxagliptin, Linagliptin, Gemigliptin, Alogliptin, Exenatide, Liraglutide, Exenatide QW, Acarbose, Voglibose, canagliflozin, ipragliflozin, exenatide, lixisenatide, liraglutide, alciglutide
Unpermitted insulin use	for up to 14 days total during the study and up to 7 continuous days is permitted
Systemic corticosteriod therapy	Hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, prednisone, Triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, halcinonide, Betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone, Hydrocortisone-17-valerate, halometasone, alclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone pivalate, fluprednidene acetate, Hydrocortisone-17-butyrate, hydrocortisone-17-aceponate, hydrocortisone-17-buteprate, ciclesonide, prednicarbate.
Medications potentially influence on bone metabolism	Anastrazole, exemestane, letrozole,leuprorelin acetate, goserelin, hydrocortisone, prednisolone Tamoxifen (premenopausal use), pioglitazone and rosiglitazone maleate, Heparin, warfarin, cyclosporine, glucocorticoids, medroxyprogesterone acetate, thyroid hormone, *Note: Assumed, these medications will have minor impact and will not impact PPS population.*
Anti-obesity medication	Any anti-obesity medicaiton
Hormone replacement therapy	Not including local treatment
Sibutramine	Sibutramine
Phentermine	Phentermine

Orlistat	Orlistat
Rimonabant	Rimonabant
Benzphetamine	Benzphetamine
Diethylpropion	Diethylpropion
Methamphetamine	Methamphetamine
Phendimetrazine	Phendimetrazine

APPENDIX 2 PROGRAMMING CONVENTIONS FOR OUTPUTS

Dates & Times

Depending on data available, dates and times will take the form DDMMMYYYY and HH:MM:SS.

Spelling Format

English US

Presentation of Treatment Groups

All summaries will be presented by assigned dose level. Dose expansion phase subjects will be included in their dose level group, and presented together with dose escalation subjects receiving the same dose level.

Treatment Group	For Tables, Listings and Graphs
Dapagliflozin 10 mg QD	TrtD
Glimepiride 1 to 2 mg QD	TrtG
Screen failures (in listings only)	SF
Untreated eligible subjects (in listings only)	NOTTRT

Presenting Order

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

- center-subject ID,
- Treatment group, in the order as above table,
- date (where applicable)

All tables containing coded terms (CM, MH, AE, etc), coded records will be sorted in alphabetic order.