AstraZeneca

A clinical pharmacology and long term study to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of dapagliflozin therapy in combination with insulin in Japanese subjects with type 1 diabetes who have inadequate glycemic control

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACE-I	Angiotensin-converting-enzyme inhibitor
ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AT	Amniotransferase ; short for ALT or AST
AZDD	AZ Drug Dictionary
BMI	Body mass index
CRF	Case Report Form (electronic/paper)
CSII	Continuous subcutaneous insulin infusion
DAE	Discontinuation of study drug
DBP	Diastolic blood pressrue
DKA	Diabetic ketoacidosis
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FAS-b	Full analysis set –Part B
GA	Glycoalbumin
HABA1C	Hemoglobin A1c (glycated hemoglobin)
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
MA	Marked Abnormality
MDG	Mean Daily Glucose
MDI	Multiple daily injection
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model with Repeated Measures
MPDG	Mean postprandial daily glucose
PT	Preferred term
QD	qd quaque die, once daily
SAE	Serious adverse events

Abbreviation or special term	Explanation
SAF-B	Safety set –Part B
SD	Standard deviation
SMBG	Self monitored blood glucose
SMQ	Standardized MedDRA Queries
SOC	System organ class
T1DM	Type 1 diabetes mellitus
TSH	Thyroid Stimulating Hormone
UACR	Urinary albumin creatinin ratio
ULN	Upper limit of normal
WOCBP	Women of Childbearing Potential

1.   STUDY DETAILS

The present Statistical Analysis Plan (SAP) refers to the ***Part B*** of the study D1695C00001.

1.1   Study objectives

Objectives for Part B this study are as follows:

Primary Objective:	Outcome Measure:
[Part B] To evaluate safety and tolerability of long-term treatment (52 weeks) of dapagliflozin 5mg and 10 mg in Japanese patients with T1DM with inadequate glycemic control under standard insulin therapy.	Adverse event (including AEs of hypoglycemia and diabetic ketoacidosis (DKA) events), physical examination, vital signs (blood pressure, heart rate), ECG, and clinical laboratory measures, urine test.

Secondary Objective:	Outcome Measure:
[Part B] To assess the efficacy of long-term treatment (52 weeks) of dapagliflozin 5mg and 10 mg in Japanese patients with T1DM inadequately controlled on insulin therapy.	Change from baseline in HbA1c at Week 24 and 52 Change from baseline in glycoalbumin (GA) at Week 24 and 52 Change from baseline in average glucose values measured by 6-point self-monitored blood glucose (SMBG) at Week 24 and 52 Change from baseline in postprandial glucose values measured by 6-point SMBG at Week 24 and 52 Percent change from baseline in total daily insulin dose at Week 24 and 52 Percent change from baseline in body weight at Week 24 and 52 Proportion of subjects with HbA1c reduction from baseline of at least 0.5% without severe hypoglycaemia at Week 24 and 52 Proportion of subjects with HbA1c reduction from baseline of at least 0.5% at Week 24 and 52 Proportion of subjects with HbA1c < 7.0% at Week 24 and 52 Change from baseline to Week 24 and 52 in seated SBP among subjects with hypertension at baseline, defined as seated SBP $\geq$ 140 mmHg and/or seated DBP $\geq$ 90 mmHg

Exploratory Objective:	Outcome Measure:
[Part B] The efficacy evaluation will be made by comparing subgroups BMI <25.0 kg/m^2 or BMI ≥ 25.0 kg/m^2.	Change from baseline in HbA1c, GA, average/post-prandial glucose values measured by 6-point SMBG, and percent change from baseline in body weight, total daily insulin dose by subgroup defined by BMI.

1.2   Study design

The study design of Part B is a randomized, open-label, 2 arm, parallel-group design. One hundred forty Japanese subjects in total will be randomized in a 1:1 ratio into one of the two treatment arms; dapagliflozin 5 mg or dapagliflozin 10 mg.

Potential subjects who will join the study from part B will be assessed for eligibility criteria at the screening visit. A wash-out period is applicable only for subjects who received α-GI at enrolment or within one month before enrolment. Eligible subjects who are treated with insulin only, will skip the period and directly proceed to the randomization. On Day 1, subjects who meet all the protocol-specific enrolment and randomization inclusion criteria and meet none of the exclusion criteria will be randomized into one of the 2 open-label treatment arms (dapagliflozin 5 mg QD or dapagliflozin 10 mg QD) in a 1:1 ratio. Randomization will be stratified by the following factor to ensure equal representation across all treatment groups:

- HbA1c < 9.0% vs. ≥ 9.0% at screening visit

Subjects will receive dapagliflozin 5 mg QD or 10 mg QD for 52 weeks, and a 4-week follow-up evaluation. Besides study medications, subjects will be treated with MDI (3 or more injections per day of basal and bolus insulin) or CSII.

The study design schematic is presented in Figure 1. Study assessment schedule is presented in Table 1.

Figure 1   Study Design Schematic (Part B)

Screening Visit		Treatment period																Follow-up period

Wash-out period [a]

E   R   d

Insulin therapy

dapagliflozin 5 mg once daily

dapagliflozin 10 mg once daily

R

Week	-3	-1	0[b]	1	2[c]	4	8	12	16	20	24	32	40	48	52	56
Visit	1	2	3	4 (5)	6	7	8	9	10	11	12	13	14	15	16
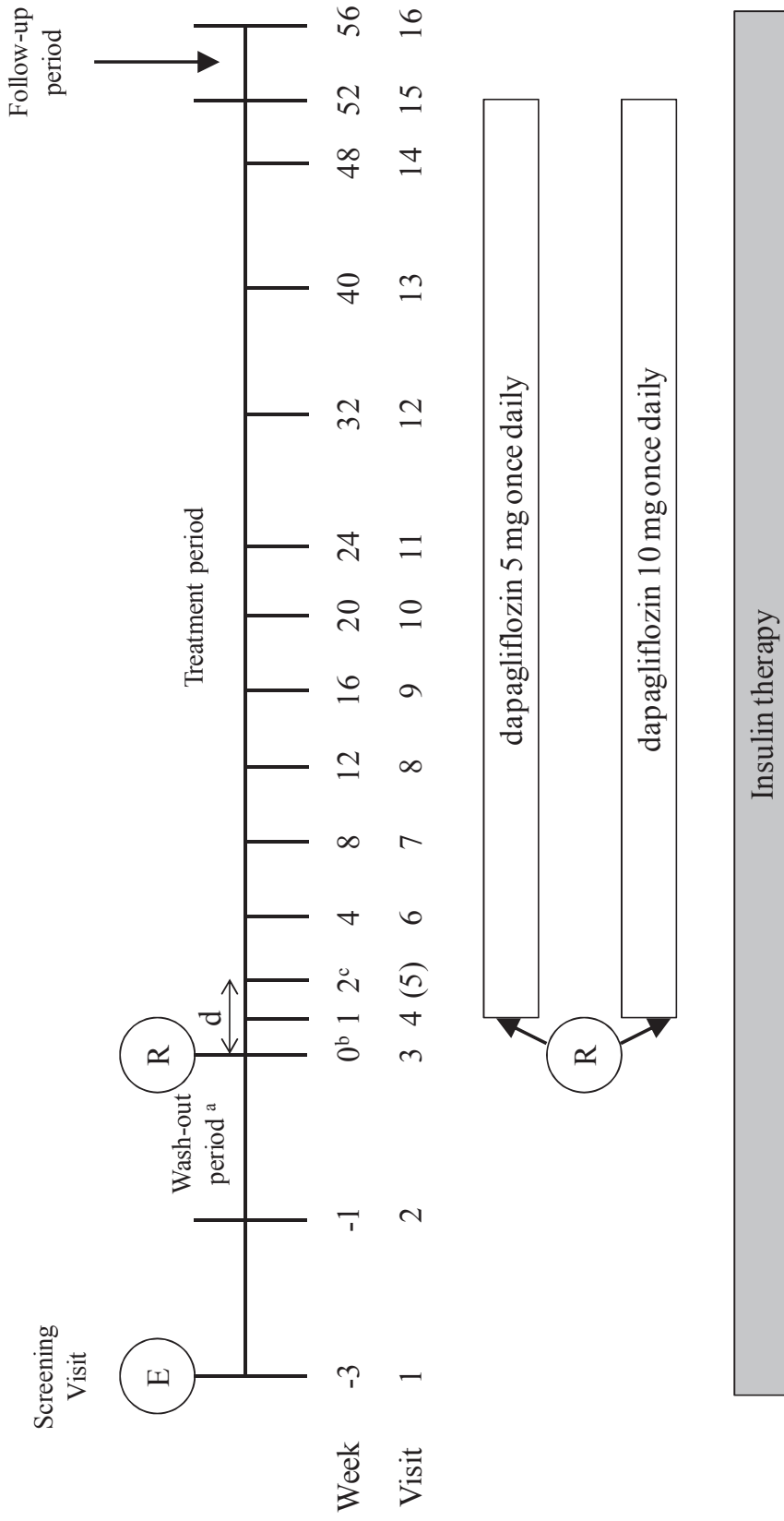
E: Enrolment; R; Randomization

a   Wash-out period is applicable only for subjects who are on an α-GI at enrolment or within one month before enrolment. Subjects on insulin only as their diabetes treatment will skip the period and directly proceed to the Visit 3.

B   Day 1 of Week 0 means the stating day of dapagliflozin.

C   Either hospital visit or telephone contact is acceptable for visit at Week 2.

D   On Day 2, 4 and 10 patients must contact the Investigators by phone and report the patient's condition (including glucose and ketone values from SMBG). The investigators must indicate appropriate insulin adjustment. There is time window ± 1 day for Day 4 and 10.

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Table 1   Study schedule (Part B)

Period	Screening	Wash-out[a]	Treatment period										Follow-up period[d]	
Week	-3	-1	0[b]	1	2[c]	4	8	12	16	20	24	32, 40, 48	52	56
Visit	1	2	3	4	(5)	6	7	8	9	10	11	12, 13, 14	15	16
Visit window (days)	-7	±3	0	0	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Eligibility Assessments														
Informed Consent[e]	X													
Review Inclusion/Exclusion	X	X												
Review Medical History	X	X												
General procedures														
Telephone contact (TC)[f]				←——————→										
Complete Physical Examination	X													
Brief Physical Examination		X	X			X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR), Body Weight	X	X	X			X	X	X	X	X	X	X	X	X
Height	X													
12-lead ECG	X										X		X	X
Weight (BMI)	X	X	X	X		X	X	X	X	X	X	X	X	X
Review concomitant medications/ procedures	X	X	X	X		X	X	X	X	X	X	X	X	X
Provide Dietary and Exercise Counselling	X	X	X			X	X	X	X	X	X	X	X	

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Table 1   Study schedule (Part B)

Period	Screening	Wash-out[a]	Treatment period											Follow-up period[d]
Week	-3	-1	0[b]	1	2[c]	4	8	12	16	20	24	32, 40, 48	52	56
Visit	1	2	3	4	(5)	6	7	8	9	10	11	12, 13, 14	15	16
Visit window (days)	-7	±3	0	0	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Dispense subject diaries, blood glucose/ketone meters and provide instructions	X	X	X									X		
Review subject diaries		X	X	X		X	X	X	X	X	X	X		X
Adjust Insulin Dose, as needed	◄──►													
Safety Assessments														
Assess Adverse Events	◄──►													
Assess Hypoglycemia Episodes	◄──►													
Assess Diabetic Ketoacidosis	◄──►													
SMBG 4 point			◄───►											
Laboratory Assessments														
C-peptide	X													
Hepatitis Screen Panel	X													
TSH	X													
Blood Standard Safety Laboratory Panel	X		X			X	X	X	X	X	X	X	X	X

Table 1   Study schedule (Part B)

Period	Screening	Wash-out[a]	Treatment period										Follow-up period[d]	
Week	**-3**	**-1**	**0[b]**	**1**	**2[c]**	**4**	**8**	**12**	**16**	**20**	**24**	**32, 40, 48**	**52**	**56**
Visit	**1**	**2**	**3**	**4**	**(5)**	**6**	**7**	**8**	**9**	**10**	**11**	**12, 13, 14**	**15**	**16**
Visit window (days)	**-7**	**±3**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**
Urine Standard Safety Laboratory Panel	X		X			X	X	X	X	X	X	X	X	X
Pregnancy test (serum) WOCBP only	X													
Pregnancy test (urine) WOCBP only			X			X	X	X	X	X	X	X	X	X
Urine (dipstick)	X		X			X	X		X		X	X	X	X
Microscopic urinalysis	X		X							X	X	X	X	X
6point SMBG, Self-Monitored Blood Ketone			X[g]					X[g]			X[g]		X[g]	
HbA1c, GA	X		X			X	X	X	X	X	X	X	X	
Study Drug Supply														
Randomization			X											
Dispense Study Drug			X			X	X	X	X	X	X	X		
Contact IWRS	X		X											
Review study drug dosing				X	X	X	X	X	X	X	X	X	X	

a Wash-out period is applicable only for subjects who received α-GI until enrolment. Subjects not taking other anti-hyperglycemic drugs other than insulin skip the period and directly proceed to the Treatment period.

B Day 1 of Week 0 means the stating day of dapagliflozin. The previous day of Day 1 is shown as "Day -1"

c Either hospital visit or telephone contact is acceptable on Week 2.

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D   If a patient meet any study discontinuation criteria, the patient should receive the Week 52 and follow-up evaluation.

E   If a patient performed Informed Consent only, it is to allowed be out of visit window.

F   On Day 2, 4 (± 1 day) and 10 (± 1 day) patients must contact the Investigators by phone and report the patient's condition (including glucose and ketone values from SMBG). The Investigators must indicate appropriate insulin adjustment.

G   It will be performed on any 3 days within a week before each visit

1.3 Number of subjects

The number of patients in the Long term treatment part was decided according to the ICH E1 guideline (1994), "The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions". The number of patients in the Part B was designed so that approximately 100 Japanese T1DM patients treated by dapagliflozin 5 mg and 10 mg for 52 weeks are secured in total, when summed up with Japanese T1DM patients randomized in study MB102230, where about 160 Japanese T1DM patients are to be randomized to dapagliflozin 5 mg, 10 mg or placebo in ratio 1:1:1.

With 140 patients randomized to dapagliflozin 5 mg or 10 mg in Part B of this study, approximately 59 patients/arm are expected to complete 52-week dapagliflozin treatment in this study, assuming drop-out rate of 15%.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Enrolled set – Part B

The enrolled set includes data collected from all subjects who signed informed consent.

2.1.2 Randomized set – Part B

The randomized set includes data collected from all subjects who received a randomization number.

2.1.3 Safety analysis set – Part B (SAF-B)

The safety analysis set will include all subjects who received at least one dose of study medication for Part B and who provide any safety records. Subjects will be analysed according to the treatment group for the study medication which they received.

In case a subject did not receive the treatment as assigned by randomization (or received study medication but were not randomized), then the safety data for that subject will be presented by the first study medication administered.

2.1.4 Full analysis set – Part B (FAS-B)

The full analysis set will include all randomized subject who received at least one dose of randomized study medication for Part B, and who have a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable. The subjects will be analysed according to the treatment group to which they were randomized, regardless of the actual treatment administered.

2.2 Violations and deviations

Protocol deviations will be reviewed by the study team prior to database lock. Subjects who deviate from important protocol conditions (e.g., selected inclusion/exclusion criteria) will be reported as having major (or significant) protocol deviations.

There will be no data exclusion associated with major protocol deviations in Part B of this study. Subjects having major protocol deviations will be presented by treatment group. Major protocol deviations are given in (but not limited to) Appendix 9.3.

In the unlikely case that a subject did not provide signed and dated written informed consent this subject will be excluded from all summaries.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary variables (Safety)

Safety of long-term dapagliflozin (5mg or 10 mg) treatment when coadministered with flexible insulin regimen in T1DM subjects in Part B of this study will be evaluated by the following safety measures:

- Adverse events (including hypoglycemia / DKA)

- Serious adverse events (SAEs)

- Adverse event leading to discontinuation of study drug (DAEs)

- Vital signs

- ECG

- Clinical laboratory measures(including urine test)

3.2 Secondary variables (Efficacy)

Efficacy of long-term dapagliflozin (5mg or 10 mg) treatment when co-administered with flexible insulin regimen in T1DM subjects in Part B of this study will be evaluated by the following efficacy measures:

- Change from baseline in HbA1c at Week 24 and 52
- Change from baseline in GA at Week 24 and 52
- Change from baseline in average glucose values measured by 6-point SMBG at Week 24 and 52
- Change from baseline in post-prandial glucose values measured by 6-point SMBG at Week 24 and 52

- Percent change from baseline in total daily insulin dose at Week 24 and 52

- Percent change from baseline in body weight at Week 24 and 52

- Proportion of subjects with HbA1c reduction from baseline of at least 0.5% without severe hypoglycemia at Week 24 and 52

- Proportion of subjects with HbA1c reduction from baseline of at least 0.5% at Week 24 and 52

- Proportion of subjects with HbA1c < 7.0% at Week 24 and 52

- Change from baseline to Week 24 and 52 in seated SBP among subjects with hypertension at baseline, defined as seated SBP ≥ 140 mmHg and/or seated DBP ≥ 90 mmHg

4. ANALYSIS METHODS

4.1 General principles

4.1.1 Objectives and hypotheses

Objectives of this study are assessing the safety, tolerability, and efficacy of long-term dapagliflozin (5mg or 10 mg) treatment up to 52 weeks when co-administered with adjustable insulin regimen. No formal hypothesis testing will be performed.

4.1.2 Definitions

4.1.2.1 Baseline value

For each subject, baseline value of a parameter is defined as the last assessment of that parameter on or prior to the date of the first dose of study medication.

For measurements referring to multiple data collections during a day (i.e. 6-point measurement parameters) or to 24-hour collection periods (i.e. daily insulin dose), baseline values are considered as the available assessments of that parameter prior to the date of the first dose of the study medication.

For measurements collected over several days during the same visit window (i.e. 6-point measurement parameters, daily insulin dose), please refer to the algorithm outlined in Section 6.3 in order to define the baseline value.

4.1.2.2 Change and percent change from baseline

Change from baseline to any Week t in treatment period is defined as follows:

$$C_{Week\ t} = M_{Week\ t} - M_{baseline},$$

where:

- $C_{Week\ t}$ is the change from baseline at Week t,

- $M_{Week\ t}$ is the measurement at Week t,

- $M_{baseline}$ is the measurement at baseline.

Percent change from baseline to any Week t in treatment period is defined as follows:

$$P_{Week\ t} = 100 \times (M_{Week\ t} - M_{baseline}) / M_{baseline}.$$

Where $P_{Week\ t}$ is the percent change from baseline at Week t, and $M_{Week\ t}$ and $M_{baseline}$ are defined as above.

For analyses of parameters in terms of percent change from baseline at Week t, values will first be transformed to natural logarithms (Ln) and the results will be expressed as geometric mean percent changes from baseline. Analysis will be performed using the logarithms of the post-baseline to baseline ratios. Subsequently, the estimates from the analysis will be back transformed to original values for reporting in the tables using the formulae detailed in Table 2.

Table 2   Formulae Used to Transform Back the Results onto the Original Scale

Quantity	Computation method
Mean percent change from baseline	100 × [exp(mean change from baseline in natural logarithm) – 1]
Standard error of mean percent change from baseline	100 × exp(mean change from baseline in natural logarithm) × standard error of mean change from baseline in natural logarithm – or, equivalently – 100 × Geometric mean of the Week t to baseline ratio × standard error of mean change from baseline in natural logarithm
Lower confidence limit for mean percent change from baseline	100 × [exp(lower confidence limit for mean change from baseline in natural logarithm) – 1]
Upper confidence limit for mean percent change from baseline	100 × [exp(upper confidence limit for mean change from baseline in natural logarithm) – 1]
Adjusted mean percent change from baseline	100 × [exp(Adjusted mean change from baseline in natural logarithm) – 1]

Quantity	Computation method
Standard error of adjusted mean percent change from baseline	$100 \times \exp$(Adjusted mean change from baseline in natural logarithm) $\times$ standard error of mean change from baseline in natural logarithm
	– or, equivalently –
	$100 \times$ adjusted geometric mean of the Week t to baseline ratio $\times$ standard error of mean change from baseline in natural logarithm
Lower confidence limit for adjusted mean percent change from baseline	$100 \times$ [exp(lower confidence limit for adjusted mean change from baseline in natural logarithm) – 1]
Upper confidence limit for adjusted mean percent change from baseline	$100 \times$ [exp(upper confidence limit for adjusted mean change from baseline in natural logarithm) – 1]

4.1.2.3 Insulin up-titration more than 25% than baseline

Insulin dose for bolus and basal quantities will be collected as weekly ranges (minimum and maximum value of total daily dose over a weekly interval) during the study duration and total daily quantities (total daily basal, total daily bolus and pre-mixed separately) for limited number of days that will be used for analysis. For those days that the total daily bolus and total basal quantities are reported separately, the total daily insulin dose will be calculated by summing up the bolus and basal quantity for the same day. If either bolus or basal for the same day are missing, then the total daily will not be calculated for that day.

The minimum and maximum value for each week will be calculated by combining the non-missing information from the weekly data collection intervals together with the information from the daily data collection intervals. The midpoint (= (maximum+ minimum)/2) of the range for each week will be calculated. If for two consecutive weeks the midpoint value is 25% higher than the baseline value, then this would qualify as up-titration more than 25%. The starting time point of the up-titration is considered to be the first day of the first of the two consecutive weeks. The baseline value for this calculation will be defined as the midpoint of the last week (defined as the last 7 days) prior to randomization date or first dose date of study medication, whichever is earlier. During this interval, insulin is collected daily. The calculation will follow the algorithm specified above in order to derive that value that will be used to compare on study values to define insulin up-titration more than 25%.

4.1.2.4 Last Observation Carried Forward (LOCF)

In analysis of change (or percent change) from baseline as well as response endpoint at Week t LOCF, the measurement assigned as the Week t measurement will be used. If no Week t measurement is available (subject has discontinued before Week t, or measurement not taken at Week t though subject was not discontinued), the last available earlier post-baseline measurement will be used. Unless specified otherwise, all data regardless of insulin up-

titration will be used for the calculation of LOCF values. In the case that analysis would exclude data from subjects after insulin up-titration more than 25% from baseline, their last post-baseline measurement taken prior to or on the date of up-titration will be used.

4.1.2.5   Mean daily glucose of 6-point self monitored blood glucose (SMBG)

Prior to Day 1 visit, Week 12, Week 24 and Week 52/Study Termination or Early Treatment Termination, subjects must perform 6-point finger stick blood glucose monitoring (before meals, 2 hours post meal) at home for 3 days within the week of the visit. Meals are considered to be breakfast, lunch and dinner. Preprandial and postprandial measurements will be considered eligible for analysis if they occur prior to the start time of each meal and between 1.5 and 2.5 hours after the start of the meal time, respectively. The pre- and post-prandial meal glucose measurements obtained outside the time windows (prior to the meal, 1.5 to 2.5 hours after the start time of the meal) will be excluded from the summaries and analyses.

Glucose concentrations at each of the 6 time points will be averaged over the 3 days to derive the mean glucose concentrations at each of the 6 time points. The mean daily glucose (MDG) will then be calculated as the average over the average glucose concentrations at the 6 time points. The daily average data will be calculated only if at least one pair of average pre-prandial and post-prandial blood glucose values is available. Only complete pairs of the average pre-prandial and post-prandial blood glucose values will be used for the calculation. For example, if the available average time point data for a subject at a visit are pre-breakfast, post-breakfast, and pre-dinner, then the daily average will be calculated as (pre-breakfast + post-breakfast)/2.

4.1.2.6   Post-prandial glucose values of self monitored blood glucose (SMBG)

The post-prandial glucose values of SMBG readings will be those values that occur 2 hours after the start time of breakfast, lunch and dinner. Postprandial measurements will be considered eligible for analysis if they occur between 1.5 and 2.5 hours after the start of the meal time. The post-prandial measurements obtained outside the time windows (1.5 to 2.5 hours after the start time of the meal) will be excluded in the summaries and analyses. For SMBG parameters, glucose concentrations at each of the 3 post-prandial time points will be averaged, over the days of data collection, to derive the mean glucose concentrations at each of the 3 time points. The mean post-prandial daily glucose (MPDG) will then be calculated as the average over the average glucose concentrations at the 3 time points. The average of all post-prandial glucose values during a day will be used for the analysis of change in post-prandial glucose values independently of whether there is a corresponding preprandial value available.

4.1.3   Descriptive summary of continuous variables

Descriptive summaries of continuous variables in terms of change or percent change from baseline values will be provided by treatment group and overall, if applicable.

4.1.4   Descriptive summary of categorical variables

Descriptive summaries of categorical variables will consist of frequencies and percentages for

each treatment group and overall, if applicable.

4.1.5 Mixed Model for Repeated Measures (MMRM) for outcomes with single measurement per week t

A longitudinal repeated measures analysis using 'direct likelihood' will be performed. The SAS procedure PROC MIXED will be used. The dependent variable will be the change from baseline to each week t included in the model for efficacy endpoints examining changes from baseline. For analyses of parameters in terms of percent change from baseline at Week t, values will first be transformed to logarithms and the results will be expressed as geometric mean percent changes from baseline. The dependent variable will be the natural logarithms (Ln) of the post-baseline to baseline ratios. The model estimates will be back transformed to original values using the formulae detailed in Table 2.

The preferred model will include the fixed categorical effects of treatment, week, randomization stratification factor and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. Model results will only be reported if at least 10 subjects have both baseline and Week t measurements in all treatment groups. Otherwise, just mean (SD) and mean change from baseline (SD) will be displayed for Week t in the table. For parameters analyzed as percent change from baseline, the natural logarithm of the baseline values will be used in the above model specification. An unstructured matrix for the within-subject error variance covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method.

In case of non-convergence of the preferred model or memory space issues the following backup models are defined:

1) The first backup model is the same as the preferred model but the Kenward-Roger method will be replaced by Satterthwaite approximation.

2) The second backup model is the same as the preferred model but without the term for baseline measurement-by-week interaction. The second back-up model will only be provided if the first back-up model does not converge or has memory issues.

The model will provide least-squares mean estimates, standard errors and 2-sided 95% confidence intervals for mean change at all time points within treatments.

4.1.6 Mixed Model with Repeated Measures (MMRM) for outcomes with multiple measurements per week t

Some efficacy parameters (i.e. parameters from 6-point SMBG or daily insulin dose) are measured daily during a visit window. Within each visit window (including baseline and post-baseline visit windows as outlined in section 6.2) the average for all available data points will be calculated and this will constitute the baseline or Week t value (as applicable). Analysis will be performed with a longitudinal repeated measurements model as outlined in Section 4.1.5.

4.1.7 Kaplan-Meier curve and estimates for time-to-event analysis

Kaplan-Meier plots of time to event variables will be displayed by treatment group. Unless otherwise specified, the plot will be presented only when there are at least 5 events in one treatment group. Additionally, a table will accompany the plot and will display the Kaplan-Meier estimates of the cumulative proportion (with 95% CI calculated based on Greenwood's method when applicable) of subjects with event at specific time points by treatment group. If the estimated lower bound of 95% CI is below 0 or the estimated upper bound of 95% CI is over 1, then it will be restricted to 0 or 1 respectively.

4.1.8 Analysis of proportions

For proportions of responders (e.g. meeting A1C criteria) percentage (100*n/N) and 95% confidence intervals will be provided by the Clopper-Pearson method.

4.2 Analysis methods

4.2.1 Study population

4.2.1.1 Subject disposition

The disposition of subjects for the pre-randomization period, the study treatment period and safety follow-up period (where applicable) will be summarized.

The summary of status in the pre-randomization will include all subjects enrolled (who signed informed consent). The summary of status in the study treatment period will include all subjects in Randomized set, and be presented by randomized treatment group. This summary will include subjects completing and discontinuing the study treatment period with reasons for discontinuation.

Reasons for discontinuation for subjects who discontinued from the pre-randomization period and from the randomized study treatment period will be tabulated and listed.

Subjects enrolled, randomized, included in the Full analysis set and included in the Safety set will be summarized by study site.

4.2.1.2 Demographic and other baseline characteristics

Demographic and other baseline characteristics, including diabetes-related characteristics and renal function characteristics will be summarized by treatment group and overall, using the Randomized set.

Demographic and baseline characteristics are listed in Table 3. Diabetes related baseline characteristics are listed in Table 4. Renal function baseline characteristics are listed in Table 5.

All summaries of continuous characteristics will be based on non-missing observations. For categorical characteristics, percentages will be calculated out of the total number of subjects in

the data set, overall and by treatment group (i.e., each denominator includes the number of subjects with missing/unknown values for the characteristic).

Table 3   Demographic and Baseline Characteristics

Characteristic	Summarized as	Categories
Gender	Categorical	Male, Female
Age	Categorical and Continuous	< 65 yrs ≥ 65 – < 75 yrs ≥ 75 yrs
		< 35 yrs ≥ 35 - < 50 yrs ≥ 50 yrs
Female Age	Categorical	≤ 50 yrs >50 yrs
Body Weight	Continuous	-
Body Mass Index	Categorical and Continuous	< 25 kg/m2 ≥ 25 kg/m2 ≥ 27 kg/m2 ≥ 30 kg/m2

Table 4   Diabetes-Related Baseline Characteristics

Characteristic	Summarized as	Categories
Duration of Type 1 Diabetes	Categorical and Continuous	< 10 yrs ≥ 10 and ≤ 20 yrs > 20 yrs
HbA1c	Categorical and Continuous	< 8% ≥ 8 and < 9% ≥ 9%
		< 9% ≥ 9%
C-peptide*	Categorical and Continuous	< 0.1 ng/mL ≥ 0.1 ng/mL
Method of insulin administration	Categorical	Multiple Daily Injections Continuous Subcutaneous Insulin Infusion

Characteristic	Summarized as	Categories
Total daily insulin, basal insulin, bolus insulin	Continuous	
Stratum HbA1c**	Categorical	< 9% ≥ 9%

* For C-peptide values (see appendix 9.2) that will be received with an operator sign as a part of the result (below detection limit <0.1 ng/mL), a process to strip the operator sign will be applied and the resulting numeric values will be used for data analysis. The raw value with operator remained as such in the database.
** Will be used from IWRS randomization stratum

Table 5   **Baseline Renal Function**

Characteristic	Summarized as	Categories
eGFR (Japanese formula)	Categorical and Continues	< 30 mL/min/1.73 m2 ≥ 30 and < 45 mL/min/1.73 m2 ≥ 45 and < 60 mL/min/1.73 m2 ≥ 60 and < 90 mL/min/1.73 m2 ≥ 90 mL/min/1.73 m2

4.2.1.3   Specific and general disease histories

The number (percent) of subjects with diabetes, diabetes-related disease histories will be summarized by treatment group and overall using the Randomized set.

The number (percent) of subjects with general medical history findings will also be summarized by treatment group and overall using the Randomized set.

4.2.2   Extent of exposure

4.2.2.1   Study medication

The extent of exposure to study medication during the treatment period is defined as the difference between the last and the first dose of study medication of the treatment period plus 1 day. The extent of exposure to study medication will be summarized using the Safety set for the treatment period, where the number and percent of subjects with an extent of exposure within pre-specified day ranges will be presented by treatment group. The categorization for the treatment period is 1-7, 8-30, 31-60, 61-90, 91-120, 121-180, 181-270, 271-360, >360 days. The mean (SD), median and range of the number of days of exposure will also be presented.

A listing of subjects by batch number of study medication will also be generated.

In addition, the exposure in terms of total patient-years will be calculated by treatment group using the sum of the exposure to study medication of all subjects (in years) in a treatment group.

4.2.2.2   Interruption of Study Medication

Interruption of study drug is indicated by missing intervals in drug administration on the CRF.

4.2.2.3   Current and concomitant medications

Concomitant medications will be summarized using the Safety analysis set by drug class and (generic) drug name. A by-subject listing of current medications will be provided. A summary table by drug class and generic drug name will be generated for each of the following:

- all concomitant medication

- all concomitant diuretic medication

- all concomitant loop diuretic medication

- all concomitant ARB and/or ACE-I medication

- all concomitant anti-hypertensive medication

Current medications are defined as medications with a start date prior to the first day of treatment period and without a stop date prior to the consent date, i.e. current medication will be any medication with at least 1 dose taken on or after the day of consent date up to the day prior to the first dose of study medication.

Concomitant medication is defined a medication with either

- a recorded medication start date falling within the treatment period, or

- a recorded medication start date prior to the first day of study medication during the treatment period without any recorded medication stop date prior to the start of the treatment period.

This means that concomitant medications will be any medication taken from start of the treatment period up to the end of the treatment period.

Missing and partial date handling of start and stop dates of previous, current and concomitant medications, is described in Section 6.6. The AZ Drug Dictionary (AZDD) is used to code the non-study medication.

4.2.2.4   Measurement of Treatment Compliance

Percent treatment compliance is calculated treatment period for study medication. For each subject, percent compliance is defined as the number of tablets taken divided by the number of

tablets that should have been taken. A subject is considered compliant if percent compliance is ≥ 80% and ≤ 120%. The number and percent of subjects compliant during the treatment period will be displayed for the Safety set (SAF-B).

Details in calculating percent compliance are specified in Section 6.9.

4.2.3   Efficacy

This section describes the efficacy analyses as defined in secondary/exploratory objectives. The Full analysis set (FAS-B) will be used for all efficacy analyses. No formal statistical testing will be made. Estimates and two-sided 95% confidence intervals by treatment group will be provided as necessary. Unless otherwise specified, all available efficacy data obtained up to Week 52 or premature discontinuation of study drug (regardless of insulin uptitition) will be included in the analysis. For the selected efficacy variables (change from baseline in HbA1c and percent change from baseline in body weight, analyses excluding data after insulin up-titration will be performed.

4.2.3.1   Change from baseline in HbA1c (including/excluding data after insulin up-titration) at Week 24 and 52

The analysis of change from baseline in HbA1C from baseline to Week 24/52 will be based on an MMRM using 'direct likelihood' (see Section 4.1.5) and point estimates and 95% CI for the mean change within each treatment group at Week 24/52 will be calculated.

The model will be restricted to data from subjects in the Full Analysis Set who have at least one baseline assessment and any post-baseline treatment period assessment.

The above mentioned analyses will be performed regardless of insulin up-titration and excluding data after insulin up-tiration (subjects whose post-randomization insulin dose is up-titrated by more than 25% relative to baseline, measurements obtained after the first instance the 25% up-titration criteria is met will correspond to rescue and be excluded).

Descriptive summary (as specified in Section 4.1.3) of change from baseline in HbA1c over time (including/excluding data after insulin up-titration) will be also provided.

Further descriptive summary of change from baseline in HbA1c over time (including data after insulin up-titration) will be provided by subgroup as defined in Table 6.

Table 6   Subgroup factors for descriptive summary of HbA1c

Group variables	Subgroups
Gender	Female
	Male
Baseline A1c	< 9, >= 9 %
Age	< 65, 65-<75, >= 75 years
Female Age	Female <= 50 years, Female > 50 years

30

Table 6   **Subgroup factors for descriptive summary of HbA1c**

Group variables	Subgroups
Method of insulin administration	Multiple Daily Injections
	Continuous Subcutaneous Insulin Infusion
Baseline BMI	< 25, >= 25 kg/m2

4.2.3.2 Change from baseline in GA (including data after insulin up-titration) at Week 24 and 52

The analysis of change from baseline in GA from baseline to Week 24/52 will be based on an MMRM using 'direct likelihood' (see Section 4.1.5) and point estimates and 95% CI for the mean change within each treatment group at Week 24/52 will be calculated.

Descriptive summary (as specified in Section 4.1.3) of change from baseline over time (including data after insulin up-titration) will be also provided.

4.2.3.3 Change from baseline in average glucose values measured by 6-point SMBG (including data after insulin up-titration) at Week 24 and 52

See Section 4.1.2.5 for the calculation of average glucose values of 6-point SMBG.

The analysis of change from baseline in average glucose values measured by 6-point SMBG from baseline to Week 24/52 will be based on an MMRM using 'direct likelihood' (see Section 4.1.6) and point estimates and 95% CI for the mean change within each treatment group at Week 24/52 will be calculated.

Descriptive summary (as specified in Section 4.1.3) of change from baseline over time (including data after insulin up-titration) will be also provided.

Similar descriptive summary will be repeated for each of 6 time points.

4.2.3.4 Change from baseline in post-prandial glucose values measured by 6-point SMBG (including data after insulin up-titration) at Week 24 and 52

See Section 4.1.2.6 for the postprandial glucose values of 6-point SMBG.

The 6-point SMBG parameters should include capillary blood glucose values. In case that there are capillary plasma values reported, they will be converted to capillary blood equivalent values as described in Section 6.10.

The analysis of change from baseline in average glucose values measured by 6-point SMBG from baseline to Week 24/52 will be based on an MMRM using 'direct likelihood' (see Section 4.1.6) and point estimates and 95% CI for the mean change within each treatment group at Week 24/52 will be calculated.

Descriptive summary (as specified in Section 4.1.3) of change from baseline over time (including data after insulin up-titration) will be also provided.

4.2.3.5 Percent change from baseline in total daily insulin dose (including data after insulin up-titration) at Week 24 and 52

Insulin data are collected on a daily basis over 2-week periods corresponding to distinct study visits/weeks. Each data collection corresponds to insulin doses over a 24-hour period (see implications for baseline and study week definitions in Section 4.1.2.1 and Section 6.3).

Information is entered on CRF regarding the total daily bolus and basal insulin administered. The total daily insulin dose is the sum of the total daily bolus, total daily basal insulin and pre-mixed doses. If information is not available on basal or bolus insulin dose on a specific day, then the total will not be calculated for that day and it will be considered as missing to analysis.

In between those 2-week periods of total daily insulin dose data collection, insulin is reported as minimum and maximum values of total daily insulin administration over weekly intervals. The data from these weekly intervals will not be used for the analysis of secondary efficacy endpoint described in this section.

The analysis of the percent change (using logarithmic transformation for the endpoint in the model) in total daily insulin from baseline to Week 24/52 will be based on a MMRM analysis using 'direct likelihood' (see Section 4.1.5) and point estimates and 95% CI for the mean change within each treatment group at Week 24/52 will be calculated.

The same analyses will be repeated for the total daily basal and total daily bolus insulin doses. In cases that either of this information is missing on a specific day, then this information will be considered as missing for these two analyses.

Descriptive summary (as specified in Section 4.1.3) of percent change from baseline over time will be also provided.

4.2.3.6 Percent change from baseline in body weight (including/excluding data after insulin up-titration) at Week 24 and 52

Body weight is collected at selected visits during the long-term period with a single value at each visit.

The analysis of the percent change (using logarithmic transformation for the endpoint in the model) in body weight from baseline to Week 24/52 will be based on a MMRM analysis using 'direct likelihood' (see Section 4.1.5) and point estimates and 95% CI for the mean change within each treatment group at Week 24/52 will be calculated.

The above mentioned analysis of the percent change in body weight from baseline to Week 24/52 will be performed excluding data from subjects whose post-randomization insulin dose

is up-titrated by more than 25% of insulin relative to baseline and including data after insulin up-tiration.

Descriptive summary (as specified in Section 4.1.3) of percent change from baseline over time for body weight (including/excluding data after insulin up-titration) will be also provided.

4.2.3.7 Proportion of subjects with HbA1c reduction from baseline of at least 0.5% without severe hypoglycemia at Week 24 and 52 (including data after insulin up-titration)

Point estimates and 2-sided 95% confidence intervals for the proportion within each treatment group will be provided by treatment group. This analysis will be performed including data after insulin up-tiration. For missing HbA1c at Week 24/52, LOCF will be applied.

4.2.3.8 Proportion of subjects with HbA1c reduction from baseline of at least 0.5% at Week 24 and 52 (including data after insulin up-titration)

Point estimates and 2-sided 95% confidence intervals for the proportion within each treatment group will be provided by treatment group. This analysis will be performed including data after insulin up-tiration. For missing HbA1c at Week 24/52, LOCF will be applied.

4.2.3.9 Proportion of subjects with HbA1c < 7.0% at Week 24 and 52 (including data after insulin up-titration)

Point estimates and 2-sided 95% confidence intervals for the proportion within each treatment group will be provided by treatment group. This analysis will be performed including data after insulin up-tiration. For missing HbA1c at Week 24/52, LOCF will be applied.

4.2.3.10 Change from baseline to Week 24 and 52 in seated SBP (including data after insulin up-titration) among subjects with hypertension at baseline, defined as seated SBP ≥ 140 mmHg and/or seated DBP ≥ 90 mmHg

Seated systolic blood pressure is collected at selected visits with a single value at each visit.

The analysis of change from baseline in seated SBP from baseline to Week 24/52 will be based on an MMRM using 'direct likelihood' (see Section 4.1.6) and point estimates and 95% CI for the mean change within each treatment group at Week 24/52 will be calculated.

The model will be restricted to data from subjects in the Full Analysis Set who have at least one baseline assessment and any post-baseline treatment period assessment and who have hypertension at baseline (defined as seated SBP >= 140mmHg and/or seated DBP >= 90mmHg).

The above mentioned analyses will be performed including data after insulin up-tiration.

Descriptive summary (as specified in Section 4.1.3) of change from baseline over time (including data after insulin up-titration) will be also provided.

4.2.3.11   Time to Insulin up-titration by more than 25%

Time to the first post-randomization insulin up-titration by more than 25% relative to the baseline insulin dose will be presented by treatment group using a Kaplan-Meier curve using methodology described in Section 4.1.7. A plot will be presented only when there are at least 5 subjects meeting the criteria in one treatment group. An accompanying table of the cumulative proportion of subjects whose insulin was up-titrated by more than 25% from baseline at specific time points will be produced.

4.2.3.12   Descriptive summary of efficacy variables by BMI subgroup

Also, descriptive summary on various efficacy variables by baseline BMI (< 25, >= 25 kg/m2) will be provided as an exploratory analysis for following efficacy variables.

- Change from baseline in HbA1c at Week 24/52 (including data after insulin up-titration) by baseline BMI (as already mentioned in Table 6)

- Change from baseline in GA at Week 24/52 (including data after insulin up-titration) by baseline BMI

- Change from baseline in average glucose values measured by 6-point SMBG at Week 24/52 (including data after insulin up-titration) by baseline BMI

- Change from baseline in postprandial glucose values measured by 6-point SMBG at Week 24/52 (including data after insulin up-titration) by baseline BMI

- Percent change from baseline in mean total daily insulin dose (including data after insulin up-titration) at Week 24/52 by baseline BMI

- Percent change from baseline in mean daily basal insulin dose (including data after insulin up-titration) at Week 24/52 by baseline BMI

- Percent change from baseline in mean daily bolus insulin dose (including data after insulin up-titration) at Week 24/52 by baseline BMI

- Percent change from baseline in body weight (including data after insulin up-titration) at Week 24/52 by baseline BMI

4.2.4   Safety

This section describes the safety analyses as defined in primary objective. The Safety set will be used for all safety analyses. No formal statistical testing will be made and data will be presented with descriptive summary by treatment group.

Unless otherwise specified, safety analyses will include any data regardless of 25% insulin up-titration after randomization.

4.2.4.1   Adverse Events

Adverse Events (AEs) will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs will use the version of MedDRA that is current at the time of database lock for each study. No statistical test will be performed to compare adverse event rates between treatment groups. Counting rules for adverse events are described in Section 6.7.

In summaries by SOC and PT, AEs will be sorted by decreasing frequency within each SOC and PT according to the highest Dapagliflozin dose group. In summaries by PT, AEs will be sorted by decreasing frequency within PT according to the highest dapagliflozin dose group. Separate pages to capture events of hypoglycemia are contained within the CRF. Hypoglycemia or discontinuation due to hypoglycemia would not be reported on an AE CRF page unless the event fulfilled criteria for a Serious AE (SAE) in which case an SAE form would be completed. Hypoglycemia events that are reported as SAEs will be included in all summaries of AEs or SAEs. Separate summaries will be provided including hypoglycemia events reported on that special CRF pages.

All Adverse Events

All adverse events (serious and non-serious, excluding hypoglycemic events/DKA events that are not reported as SAEs) with onset during the treatment period will be summarized by SOC, PT, and treatment group. In addition, a subject listing of all reported adverse events will be produced, displaying all events (including pre-treatment events). All adverse events (serious and non-serious) including all hypoglycemic events/DKA events will also be summarized by treatment group.

AEs and SAEs with an onset from Day 1 of the treatment period up to and including 4 days and 30 days respectively, after the last dose date in the treatment period will be considered as occurring during the treatment period.

In addition, number of subjects reporting any of the following during the treatment period will be summarized for all treated subjects:

- at least one adverse event

- at least one hypoglycemia event

- at least one DKA event

- at least one AE or hypoglycemia event or DKA event

- at least one related adverse event

- deaths

- at least one SAE

- at least one related SAE

- SAE leading to discontinuation of study medication

- AE leading to discontinuation of study medication

- hypoglycemia leading to discontinuation of study medication

- DKA leading to discontinuation of study medication

In addition, the following summaries will be provided for treatment period (excluding hypoglycemic events/DKA events that are not reported as SAEs):

- Proportion of subjects with adverse events in subgroups of subjects defined by age category (< 65 and ≥ 65yrs), by gender, by female age category (≤ 50 and > 50yrs) and by baseline BMI (<25, $>= 25$ kg/m2).

- Most common adverse events by PT and treatment group (i.e., reported by $\geq 2\%$ of subjects in any treatment group),

- Non-serious adverse events by preferred term (i.e., reported by $\geq 5\%$ of subjects in any treatment group)

- Adverse events by SOC, PT, intensity and treatment group,

- Adverse events related to study medication by SOC, PT, and treatment group.

In addition to analyses of event incidence at the subject level, recurrence analyses will be performed at the event level. In order to prepare these summaries, the CRF data will be processed according to standard sponsor algorithms to categorize each line of patient data as a new occurrence or a continuation of an existing event. This determination will be based upon onset and resolution dates. Each line of patient data will represent the maximum severity observed as well as the last known assessed relationship to study medication by the investigator.

The following summary information will be provided:

Total number and rate (exposure adjusted) of occurrences for all AEs occurring in at least 5% of the subjects treated. This data will be presented as the rate per 100 years of patient exposure. Exposure to study medication will be calculated according to approved standard sponsor algorithms as well. As an example, if 5 patients report 7 unique episodes of headache and had a combined cumulative exposure of 20 years to study medication, the incidence rate is reported as 7 / 20 * (100) or 35 cases per 100 patient years of exposure.

In addition, a subject listing of all reported adverse events will be produced, displaying all events (including pre-treatment events) that occurred prior to the start date of treatment

period, if any, or in subjects who dropped-out during the treatment period. The listing will flag AE not counted as a unique AE.

For the purpose of clinical trial transparency, listing of most common non-serious AEs ($\geq$ 5 % of subjects in any treatment group) will be produced for posting at public websites (e.g., NIH's www.ClinialTrials.gov).

Deaths

All deaths recorded on the status page, the AE page, or SAE page (with a death date, cause of death, outcome or SAE categorization present) of the CRF will be considered a death in the analyses. Any deaths that occur during the study will be described in depth as narrative in the CSR. A summary table by treatment group of all deaths that occurred during the treatment period will be produced. Deaths with an onset from day 1 of treatment period up to and including 30 days after the last dose date in the treatment period will be considered as occurring during the treatment period.

Additionally a listing of all deaths that occurred occur prior to the start date of treatment period will be produced for enrolled subjects.

Serious Adverse Events

All SAEs (including hypoglycemic events) will be described in narratives, regardless of investigator assessment of causality. SAEs with an onset from Day 1 of the treatment period up to and including 30 days after the last dose date in the treatment period will be considered as occurring during the treatment period.

SAEs occurring during the treatment period will be summarized by SOC, PT, and treatment group. In addition, the proportion of subjects with related SAEs will be presented by SOC, PT, and treatment group. A listing of all SAEs will be produced, displaying all SAEs (including pre-treatment events).

Adverse Events Leading to Discontinuation of Study Medication

AEs with an onset during the treatment period reported with an action taken of discontinuation of study medication will be summarized by SOC, PT, and treatment group . This summary will include hypoglycemia events that are reported as SAEs. When summarizing AEs leading to discontinuation, no upper cutoff day windows (i.e. 4 days and 30 days from last dosing date treatment period for AEs and SAEs respectively) are applied.

In addition, a subject listing of discontinuation due to AEs will be provided, displaying all events that led to discontinuation.

4.2.4.2   Adverse Events of Special Interest

Separate summaries will be provided for the following AEs of special interest. To identify each type of AE of special interest in this section, a list of PTs will be selected before database lock. Unless otherwise specified, AEs and SAEs of special interest with an onset from Day 1

of the treatment period up to and including 4 days and 30 days respectively, after the last dose date in treatment period will be considered as occurring during the treatment period.

Hepatic adverse events

To facilitate monitoring of liver safety in subjects treated with dapagliflozin, a list of PTs were selected before database lock of the study to form the Standard MedDRA Query (SMQ) for events of hepatic disorders. The number and percentage of subjects with events of hepatic disorders will be summarized by PT and treatment group.

Genital infection

The definition of events of genital infection is based on the dapagliflozin predefined list of events.

The number and percentage of subjects with events of genital infections will be summarized by PT and treatment group in the treatment period. The number and percentage of subjects with events of genital infections will also be summarized by gender and treatment group.

The number and percentage of subjects with events of genital infection will be summarized for the subgroups defined on the basis of categorized variables including the frequency of events per subject (recurrence; 1, 2, 3 or > 3) and additional treatment (yes, no or unknown).

The number and percentage of subjects with events of genital infections qualifying as an SAE will be summarized by PT and treatment group in the treatment period.

The number and percentage of subjects with events of genital infections leading to discontinuation of study medication will be summarized by PT and treatment group.

Urinary-tract Infection

The definitions of events of urinary-tract infection and its subset of kidney infections are based on the dapagliflozin predefined list of events.

The number and percentage of subjects with events of urinary-tract infection and with kidney infections will be summarized by PT and treatment group in the treatment period. The number and percentage of subjects with urinary-tract infection will also be summarized by gender and treatment group in the treatment period.

The number and percentage of subjects with events of urinary-tract infection will be summarized for the subgroups defined on the basis of categorized variables including the frequency of events per subject (recurrence; 1, 2, 3 or > 3) and additional treatment (yes, no, or unknown).

The number and percentage of subjects with events of urinary-tract infection qualifying as an SAE will be summarized by preferred term and treatment group in the treatment period.

The number and percentage of subjects with events of urinary-tract infection leading to discontinuation of study medication will be summarized by PT and treatment group in the treatment period.

Diabetic ketoacidosis (DKA)

A DKA Adjudication Committee will independently adjudicate all the DKA events reported by the investigators and those identified based on predefined algorithm during the study period. A separate Adjudication Manual will define and describe the procedure for the handling, reporting, and classification of these cases.

DKA events with an onset from Day 1 of the treatment period up to and including 4 days after the last dose date will be considered as occurring during the treatment period. The proportion of subjects with DKA events will be tabulated both by type assigned at adjudication and overall by treatment group in the treatment period.

DKA events with an onset during the treatment period and leading to discontinuation of study medication will be summarized by treatment group. When summarizing DKA events leading to discontinuation, no upper cutoff day windows are applied.

The number and percentage of subjects with DKA events, both overall and adjudicated as definite, will be summarized by frequency of events per subject (recurrence; 1, 2, 3, > 3). The total number of events by treatment group will be summarized for the treatment period. The exposure adjusted incidence rate of DKA events (including recurrences) will be summarized by monthly intervals in order to assess any over time changes in the incidence rate.

Time to first DKA event adjudicated as definite will be presented by treatment group using a Kaplan-Meier curve using methodology described in Section 4.1.7. A plot will be presented only when there are at least 5 events in one treatment group. An accompanying table of the cumulative proportion of subjects with time to first DKA event adjudicated as definite at specific time points will be produced.

A listing of subjects will be produced and it will display all confirmed adjudicated DKA events with an onset date/time from the start date/time of study treatment.

Hypoglycemia

Separate pages to capture events of hypoglycemia are contained within the CRF. Hypoglycemic events with an onset from Day 1 of study treatment up to and including 4 days after the last dose date in treatment period will be considered as occurring during the treatment period.

Hypoglycemic events will be categorized using the following classes following ADA recommendation :

1.   **Severe hypoglycemia.** "An event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions. These episodes

may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration."

2.   **Documented symptomatic hypoglycemia.** "An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration <=70mg/dl (3.9mmol/l)."

3.   **A**symptomatic hypoglycemia. "An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70mg/dl (3.9mmol/l). Since the glycemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline is normally 65–70mg/dl (3.6–3.9mmol/l) and since antecedent plasma glucose concentrations of ≤ 70mg/dl (3.9mmol/l) reduce sympathoadrenal responses to subsequent hypoglycemia , this criterion sets the lower limit for the variation in plasma glucose in nondiabetic, nonpregnant individuals as the conservative lower limit for individuals with diabetes."

4.   **Probable symptomatic hypoglycemia.** "An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 70mg/dl [3.9mmol/l]). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is important to recognize these events as "probable" hypoglycemia. Such self-reported episodes that are not confirmed by a contemporaneous low plasma glucose determination may not be suitable outcome measures for clinical studies that are aimed at evaluating therapy, but they should be reported."

5.   **Relative hypoglycemia.** "An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration > 70mg/dl (3.9mmol/l). This category reflects the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels > 70mg/dl (3.9mmol/l) as plasma glucose concentrations decline toward that level. Though causing distress and interfering with the patient's sense of well-being, and potentially limiting the achievement of optimal glycemic control, such episodes probably pose no direct harm and therefore may not be a suitable outcome measure for clinical studies that are aimed at evaluating therapy, but they should be reported."

The above mentioned classification refers to plasma glucose measurements. In cases where whole blood glucose measurements are reported, they will be converted to plasma equivalent as described in section 6.10.

All analyses of hypoglycemic events will be performed both overall and by class of events as per ADA categorization presented above.

Hypoglycemic events with an onset during the treatment period and those leading to discontinuation of study medication will be summarized by treatment group. When summarizing hypoglycemic events leading to discontinuation no upper cutoff day windows are applied.

Time to hypoglycemic events leading to discontinuation of study medication will be presented by treatment group using a Kaplan-Meier curve using methodology described in Section 4.1.7. A plot will be presented only when there are at least 5 events in one treatment group. An accompanying table of the cumulative proportion of subjects with time to hypoglycemic events leading to discontinuation of study medication at specific time points during the treatment period will be produced.

The number and percentage of subjects with hypoglycemic events will be summarized by frequency of events (recurrence; for severe hypoglycemia: 1, 2, >=3 ; for documented symptomatic hypoglycemia: 1-3, 4-6, or >=7, for asymptomatic, probable symptomatic, relative hypoglycemia and all hypoglycemic events independently of ADA categorization: 1-5, 6-9, or >=10). The total number of events by treatment group will be summarized for the treatment period. The exposure-adjusted incidence rate of hypoglycemic events (including recurrences) will be summarized by monthly intervals in order to assess any over time changes in the incidence rate.

Volume Depletion (Hypotension/Dehydration/Hypovolemia)

The definitions of volume depletion events are based on the dapagliflozin predefined list of events. The number and percentage of subjects with hypotension/dehydration/hypovolemia events will be summarized by PT and treatment group in the treatment period.

Renal Impairment/Failure

The definitions of renal impairment/failure events are based on the dapagliflozin predefined list of events. The number and percentage of subjects with renal impairment/failure events will be summarized by PT and treatment group in the treatment period.

Fractures

The definitions of events of fracture are based on the dapagliflozin predefined list of events. The number and percentage of subjects with events of fracture will be summarized by PT and treatment group in the treatment period.

Breast Cancers

The definitions of breast cancer are based on the SMQ of such events. The number and percentage of subjects with breast cancers will be summarized by PT and treatment group in the treatment period and a corresponding listing of subjects will be provided.

Bladder Cancers

The definitions of bladder cancer are based on the SMQ of such events. The number and percentage of subjects with bladder cancers will be summarized by PT and treatment group in the treatment period and a corresponding listing of subjects will be provided.

Hypersensitivity

The definition of hypersensitivity is based on the SMQ of hypersensitivity narrow list. The number and percentage of subjects with hypersensitivity will be summarized by PT and treatment group in the treatment period and a corresponding listing of subjects will be provided.

4.2.4.3 Laboratory Evaluation

Unless otherwise specified, laboratory data obtained after the start of study medication dosing up to and including 4 days (30 days for liver function laboratory tests) after the last dosing date will be considered as obtained during the treatment period. Laboratory data obtained from the day after the last study medication + 4 days (30 days for liver function laboratory tests) up to the last visit date of the follow-up period will be considered as obtained during the follow-up period. For liver safety, a summary of proportion of subjects with elevated liver test including elevated aminotransferases (AT; alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) and total bilirubin (see Section 9.1 for definition) will be provided. In addition, a summary of proportion of subjects with elevated liver tests and/or reported AE of hepatic disorder will also be provided. For those summaries, liver test data obtained after the start of study medication dosing up to and including 30 days after the last dosing date will be considered as obtained during the treatment period. Further, a listing presenting sustained elevated liver safety abnormalities will be provided.

Listings of individual laboratory measurements by subject (including pre-treatment values and values measured during the follow-up period) will be provided upon request.

Marked Laboratory Abnormalities

Laboratory abnormalities will be evaluated based on marked abnormality (MA) values. The predefined criteria for marked abnormalities are detailed in Section 9.1. If both the baseline and on-treatment values of a parameter are beyond the same MA limit for the parameter, then the on-treatment value will be considered a MA only if it is more extreme (farther from the limit) than was the baseline value. If the baseline value is beyond the low MA limit, and the post-baseline value is beyond the high MA limit (or vice-versa), then the post-baseline value will be considered a MA.

Laboratory abnormalities occurring during the treatment period will be summarized by treatment group. In the treatment period the summaries will be presented. The direction of change (high or low) in MA will be indicated in the tables.

Additionally, for each subject with a MA for a parameter, all the subject's values of that parameter over the treatment period and the follow-up period, where applicable, will be listed.

Change from Baseline in Selected Laboratory Parameters Over Time

All analyses of laboratory data will use observed data regardless of insulin up-titration that occurs post-randomization. Visit windows are provided in Section 6.3 in order to link each laboratory test to a scheduled visit. Change from baseline during the treatment period for selected laboratory parameters will be summarized by treatment group using descriptive statistics:

- hematocrit

- hemoglobin

- red blood cell (RBC) count

- platelet count

- mean cell volume (MCV)

- mean cell hemoglobin (MCH)

- mean cell hemoglobin concentraction (MCHC)

- white blood cell (WBC) count

- total bilirubin

- alanine aminotransferase (ALT)

- alkaline phosphatase

- aspartate aminotransferase (AST)

- blood urea nitrogen (BUN)

- estimated GFR using Japan guideline equation:
  eGFR (mL/min/1.73m^2) = 194 x (Scr)$^{-1.094}$ x (Age)$^{-0.287}$ x (0.739 if female)

- creatine kinase (creatine phosphokinase) (CK)

- creatinine, serum (S$_{cr}$)

- creatinine clearance (change and percent change from baseline)

- electrolytes - sodium, potassium, bicarbonate, chloride, magnesium and calcium

- total protein, serum

- uric acid

- albumin

- inorganic phosphorus

- uric acid

- urinary albumin to creatinine ratio (UACR)

- urinary glucose to creatinine ratio

- urinary glucose

- urinary albumin

Additional Laboratory Data Summaries

For the treatment period, the following summaries will be provided.

<u>Shift Tables for Electrolytes (Sodium, Potassium, Calcium, Phosphate, and Magnesium) Categories</u>
Shift tables of Safety Set subjects with electrolytes values in categories of low, normal, and high (based on normal range of central laboratory) will be summarized by treatment group using the highest (for sodium, calcium, phosphate, and magnesium) and lowest (for sodium, potassium, and calcium) values (regardless of post-randomization insulin up-titration) obtained during the treatment period.

<u>Shift Tables for Urine Albumin Excretion Categories</u>
Shift tables of Safety Set subjects with urine albumin to creatinine ratios in 0 - < 30mg/g (normoalbuminuria), 30 - < 300mg/g (microalbuminuria), and ≥ 300mg/g (macroalbuminuria) will be summarized by treatment group using the Week 24/52 values (the last observation regardless of post-randomization insulin up-titration prior to Week 24/52 will be used if no Week 24/52 measurement is available).

Self Monitored Blood Ketone

Self monitored blood ketone (measured before breakfast meal) will be recorded on the same days as SMBG (section 4.1.2.5). Valid measurements (taken before start of breakfast meal) were averaged over 3 days for each visit before analysis. Change from baseline over time will be summarized for self monitored blood ketone values.

4.2.4.4   Vital Signs

Vital signs data obtained after the start of study medication dosing up to and including 4 days after the last dose will be considered as obtained during the treatment period.

Visit windows are provided in Section 6.3 in order to link each vital sign measurement to a scheduled visit. Measured values and changes from baseline in vital sign measurements will

be summarized by treatment group at each scheduled visit using descriptive statistics (using available data regardless of insulin up-titration for subjects in Safety Set).

4.2.4.5 Electrocardiograms

The normality/abnormality of the ECG tracing, as determined by the investigator, will be summarized using frequency tables on number of subjects who have a normal/abnormal ECG tracing at Week 24/52 of the treatment period, overall and by the ECG tracing at baseline. When the data at Week 24/52 is not available for a discontinued subject, then the last observation before discontinuation of that subject (regardless of insulin up-titration) will be used for summary.

4.2.4.6 Pregnancy Test Results

By-subject listing of pregnancy test results will be provided using Safety Set.

4.2.5 Figures and Graphs

The graphs given below will be provided (by treatment group).

Longitudinal plots:

- HbA1c adjusted mean change from baseline over time (including/excluding data after insulin up-titration)

- GA adjusted mean change from baseline over time (including data after insulin up-titration)

- Mean daily 6-point SMBG glucose (including data after insulin up-titration)

- Means daily 6-point SMBG post-prandial glucose (including data after insulin up-titration)

- Total daily insulin dose adjusted mean change from baseline over time (including data after insulin up-titration)

- Body weight adjusted mean change from baseline over time (including/excluding data after insulin up-titration)

- Mean 6-point SMBG glucose concentration by time points (before and after breakfeast, lunch, dinner)

Kaplan-Meier curve:

- Time to first insulin up-titration due to inappropriate glycemic control

- Time to discontinuation of study medication due to hypoglycemia

- Time to first event of DKA adjudicated as definite

Kaplan-Meier plots will be provided only when there are at least 5 events in one treatment group.

5.   INTERIM ANALYSES – NOT APPLICABLE