AstraZeneca

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A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase III study to Evaluate the Glycemic Efficacy and Renal Safety of Dapagliflozin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment (CKD 3A) who have Inadequate Glycemic Control

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Study Statistician

PPD

09 Nov 2017
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PPD

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PPD

08 Nov 2017

Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACE-I	Angiotensin converting enzyme inhibitors
AE	Adverse Event
ALK-P	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blockers
AST	Aspartate Aminotransferase
AUA	American Urological Association
AZRand	AZ Randomization system
BMI	Body Mass Index
BP	Blood Pressure
C	Conventional Units
CKD	Chronic Kidney Disease
CR	Copy Reference
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Cardiovascular
DAE	Adverse Events Leading to Discontinuation of Study Medication
DB	Double-blind
DBP	Diastolic Blood Pressure
DILI	Drug-Induced Liver Injury
DKA	Diabetic ketoacidosis
DM	Diabetes Mellitus

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
E-code	CCI [redacted]
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
CCI [redacted]	
FPG	Fasting Plasma Glucose
FU	Follow-Up
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
GMP	Good Manufacturing Practice
Grand	Global Randomization system
Hb	Haemoglobin
HbA1c	Glycosylated Haemoglobin
CCI [redacted]	
HF	Heart Failure
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IRB	Institutional Review Board
IP	Investigational Product
KG	Kilogram
CCI [redacted]	
LSM	Least Square Mean
IMPACT	Clinical Trial Management System
IVRS	Interactive Voice Response System

Abbreviation or special term	Explanation
IWRS	Interactive Web Response System
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI-RD	Multiple Imputation on Randomized Set
MMRM	Mixed-effects Model for Repeated Measures
MNAR	Missing not at Random
MG	Milligram
NYHA	New York Heart Association
OAD	Oral Anti-diabetic Drug
PI	Principal Investigator
PPG	Post-Prandial Glucose
PTH	Parathyroid Hormone
RPD	Relevant Protocol Deviation
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
sCr	Serum Creatinine
SD	Standard Deviation
SGLT2	Sodium Glucose Co-Transporter 2
SI	International System of Units
SU	Sulfonylurea
T2DM	Type 2 Diabetes Mellitus
TB	Total Bilirubin
CCI	[redacted]
TIA	Transient Ischemic Attack
TZD	Thiazolidinedione
CCI	[redacted]

Abbreviation or special term	Explanation
CCI	[redacted]
ULN	Upper Limit Of Normal
US	United States
UTI	Urinary Tract Infection
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

AMENDMENT HISTORY

Version	Date	Brief description of change
1.1	15JUN2015	Removed baseline x treatment x week interaction term from Model 4.1.4.2
1.2	27APR2016	Added Tipping Point Analysis section, Placebo-based imputation and Dropout Reason-based Multiple Imputation for sensitivity analyses on primary efficacy analysis Added proportion of patients with missing HbA1c summary into sensitivity analysis
		Moved the analysis of Repeated Measures mixed model of change from baseline to Week 24 (regardless of rescue, with an additional indicator for rescue use) from sensitivity analysis to exploratory analysis. Added MMRM regardless of rescue or treatment discontinuation into sensitivity analysis
		In section 4.3.2 Post-Dosing Efficacy Observations, added (CCI SBP, eGFR, exploratory, insulin) to keep consistency with SAP for Dapa 23.
		Modified the description for proportional analysis in section 4.1.9 Proportion of Patients with Pre-Defined Characteristics. The new approach by Zhang 2008 will be performed.
		In Table 2, Days are adjusted to be same as the amended protocol.
		In section of Double Blind Treatment Period (V4 to V8, 24 weeks), changed OADs description to be aligned with protocol amendment v2.0.
		In section of Rescue Medication Due to Lack of Glycemic Control, added GLP-1 agonist to exception list to be aligned with protocol amendment v2.0.
		Removed all notations in Section 4.1; Added model effects description for percent change from baseline analysis.
		Removed summary of Creatine Clearance, as it's not mentioned in the CSP. The physician confirmed eGFR would be used instead.
		Removed Hy's law to be aligned with protocol amendment v2.0.

Version	Date	Brief description of change
		Removed section of Changes of Analysis from Protocol as CSP has modified for those parts.
		Modified Table 1 Exploratory objectives and outcome measures to be aligned with protocol amendment v2.0.
		Removed Appendix A2 (Important Protocol Deviation criteria); Only keep Relevant Protocol Deviation in SAP which will be programmed. Important Protocol Deviation will be from IMPACT report and will be kept in a separate document. Modified Section 2.3 Protocol Deviation accordingly.
		Updated Estimands in Table 9
		In section 1.1.1 Primary Objective, changed inclusion criteria for HbA1c from ≤10.5% to ≤11%, based on protocol amendment 3.0.
		In section 1.2 Study Design, changed from The study will be an international multi-centre study at approximately 55 centres (Canada, United States (US), Italy, Spain and Sweden). To The study will be an international multi-centre study at approximately 100 centres from countries across North America and European regions. Based on protocol amendment 3.0.
		The section 1.2 and Table 3 within that section have been updated for eGFR inclusion criteria modification based on protocol amendment 3.0 (remove average calculation between V2 and V3)
		In section 2.1.1 Enrolled Patients Set, added text about how to handle re-screened patients due to protocol amendment 3.0.
		In In section 4.2.6.2 Sensitivity Analysis, added a new sensitivity analysis with adjustment of the primary analysis estimand for both baseline HbA1c and baseline eGFR, to be aligned with protocol amendment 3.0.
		In Appendix B, Geographic Regions, added new countries.
		Updated section 6, Changes analyses from protocol, as there are CSP amendments.

Version	Date	Brief description of change
		For Proportion of patients with pre-defined characteristics analyses, deleted reference of Tsiatis et al 2008 and Zhang et al 2008. The logistic regression model will be used for proportional analyses.
		Updated Appendix A: Added HbA1c criteria at Visit 1 Added Patient changed the dose of OADs, insulin anti-hypertensive drugs, (change outside ±10%), for ≥7 consecutive days during the single-blind lead-in and double-blind treatment period
1.3	24JUN2016	Replaces all "Relevant Protocol Deviations" to "Important Protocol Deviations".
		Removed Appendix B: SAS programming to perform sensitivity analyses using PROC MI
		Demographic and Baseline Characteristics summaries reduced to Randomized Analysis Set.
		In section 4.2.6.5, modified exploratory analysis on percent change from baseline in CCI Changed from MMRM subgroup analysis to MMRM based on different subset population.
		Added Section 4.3.10 Missing Insulin dose
	19AUG2016	In section 4.2.7 AE of special interests, removed some items which were regarded as not necessary by the team.
	20OCT2016	Added section 1.1.5 Adjudication cases summarization
	24JAN2017	Table 9, removed analysis for Repeated measures mixed model of ΔhbA1c to Week 24 (regardless of rescue but prior to treatment discontinuation, with an additional indicator for rescue use)
	30JAN2017	For proportional analysis using the logistic regression model, the estimated odds ratio will be presented instead of the difference of the proportion between the treatment.
	9FEB2017	Section 2.2.1: Added "Unblinding of data will be done between declaring "Clean File" and "Final Database lock"" to clarify the time point of the data unblinding.
		Section 4.1.9: Added the description about pooling strata in logistic regression analysis.
2.0	28MAY2017	Update section 4.1.7 for sensitivity analysis for missing data CCI Added text for subgroup analysis with small strata

Version	Date	Brief description of change
	09AUG2017	Removed Sections 4.1.7.1 and 4.1.7.2 for Placebo-Based Multiple Imputation and Tipping Point analysis from the SAP. Section 4.1.7.: Updated the seed for imputation[redacted]
2.1	21SEP2017	Section 4.2.7.2 and Appendix C: Added 2 units (SI and C) for laboratory parameters where required.
2.2	27SEP2017	When only laboratory parameter unit is needed, the unit presented will be SI, except for [redacted] which will be presented as CV- section 4.2.7.2 and appendix C
	23OCT2017	Updated 4.2.7.1.6.1 Hypoglycemia to add commas to be explicit in the definition of events of hypoglycemia. Updated to add ranges for conventional units in Appendix C. Updated IPD 3 to remove "or beyond 40 – 65 mL/minute/1.73 m^2 at Visit 2" as agreed with AstraZeneca Study Physician Updated as per the comments provided by AstraZeneca in "Reconciliation report for Statistical Analysis Plan Edition 2" on 6th Oct 2017

1. STUDY DETAILS

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective is to compare the mean change from baseline in HbA1c between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes who have inadequate glycemic control, defined as HbA1c ≥7.0% but ≤11% at Visit 1, and CKD stage 3A (eGFR 45 to 59 mL/min/1.73 m^2, inclusive, at Visit 1, or Visit 2, or Visit 3 and eGFR 40 to 65 mL/min/1.73 m^2, inclusive, at Visit 1).

1.1.2 Secondary Objectives

The secondary objectives are to compare dapagliflozin 10 mg and placebo after 24 weeks (or prior to rescue) of oral administration of double-blind therapy for the following:

- The percent change from baseline in total body weight at Week 24
- The change from baseline in FPG at Week 24
- The change from baseline in seated SBP at Week 24

1.1.3 Safety Objective

The safety objectives include:

- To examine eGFR changes during the study and 3-week post-treatment for dapagliflozin 10 mg and placebo.
- To assess the proportion of patients discontinued from study medication because of worsening renal insufficiency (defined as patients reaching confirmed eGFR levels <30 mL/min/1.73 m^2) between dapagliflozin 10 mg and placebo.
- To evaluate the safety and tolerability of dapagliflozin 10 mg once daily in type 2 diabetes and CKD stage 3A.

1.1.4 Exploratory Objectives

Exploratory objectives aim to investigate the treatment difference between dapagliflozin compared with placebo when added to current background therapy in patients with T2DM and CKD3A, for the parameters listed in Table 1.

Table 1 Exploratory objectives and outcome measures

Exploratory Objective:	Outcome Measure :
CCI [redacted]	

Table 1 Exploratory objectives and outcome measures

Exploratory Objective:	Outcome Measure :
CCI [redacted]	

Table 1 Exploratory objectives and outcome measures

Exploratory Objective:	Outcome Measure :
CCI	[redacted]

Table 1 Exploratory objectives and outcome measures

Exploratory Objective:	Outcome Measure :
CCI	

1.1.5 Adjudication cases summarization

Pre-defined liver enzyme elevations will undergo adjudication. Adjudicated results will be summarized by treatment group. Liver abnormalities submitted for review by the hepatic adjudication committee will be listed.

All potential events of DKA will be recorded in the eCRF and submitted to an independent DKA Adjudication Committee. Adjudicated results will be summarized by treatment group. DKA events submitted for review by the DKA adjudication committee will be listed.

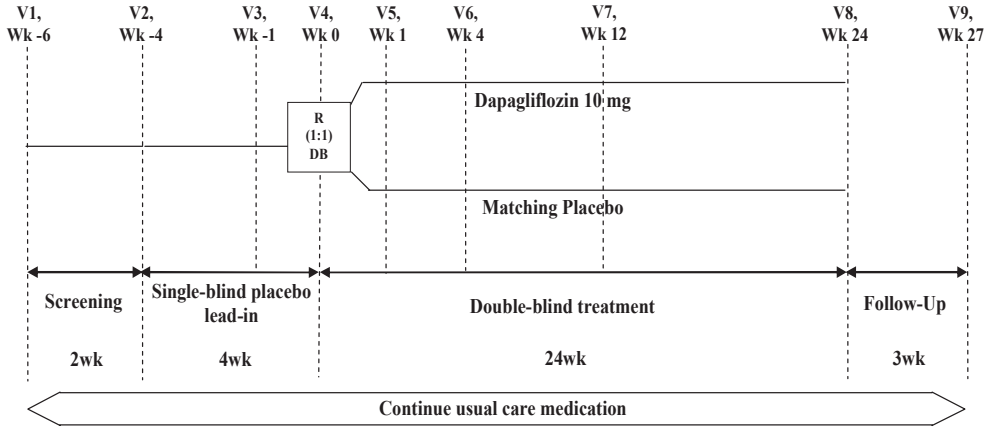
1.2 Study Design

This is a confirmatory, phase III, randomized, double-blind, 2-arm, parallel group, placebo-controlled, multi-national, multi-centre study to evaluate the clinical efficacy and safety of dapagliflozin in patients with type 2 diabetes and CKD stage 3A.

The study consists of 2-week screening period, a 4-week single-blind placebo lead-in period, a 24-week double-blind placebo-controlled treatment period, and a 3-week follow-up period. Patients will be randomized to 24 weeks treatment with dapagliflozin 10 mg or matching placebo after the placebo lead-in period. Figure 1 illustrates details on timing of visits. Table 2 provides details on schedule of study procedures.

The study will be an international multi-centre study at approximately 100 centres from countries across North America and European regions.

Figure 1 Study flow chart



R = Randomization, DB = Double-blind, V = Visit, Wk = Week

Table 2 Study Plan detailing the procedures

Study Period	**Screening period**	**Lead-in period**		**Treatment period**					**Follow-up period**
Visit	**Enrolment**	**Start of lead-in**	**Lead-in**	**Random-ization**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**End of Treatment/ Discontinuat-ion/Rescue**	**Follow-up**
Visit Number (Fasting/Non-fasting)	**1**[a] Non-fasting	**2**[b] Fasting	**3**[c] Fasting	**4**[c,d] Fasting	**5**[c,d,e] Non-fasting	**6**[c,d,e] Fasting	**7**[c,d,e] Fasting	**8**[c,d,e] Fasting	**9** Fasting
Week	**-6**	**-4**	**-1**	**0**	**1**	**4**	**12**	**24**	**27**
Day	**-42 to -29**	**-28**	**-7**	**1**	**8**	**29**	**85**	**169**	**190**
Visit Window		**± 3**	**± 3**	**± 0**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**
Signed and Dated Informed consent[f]	X								
Inclusion/Exclusion Criteria	X	X		X[g,h]					
Allocation of E-code via IVRS/IWRS	X								
Randomization to study treatment via IVRS/IWRS				X					
Demographics	X								
Medical and Surgical History	X								
Brief Physical Examination[i]	X			X		X	X		X
Complete Physical Examination[j]		X						X	
Height	X								
Weight	X	X	X	X	X	X	X	X	X
CCI [redacted]				X	X	X	X	X	

Study Period	**Screening period**	**Lead-in period**		**Treatment period**					**Follow-up period**
Visit	**Enrolment**	**Start of lead-in**	**Lead-in**	**Random-ization**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**End of Treatment/ Discontinuat-ion/Rescue**	**Follow-up**
Visit Number (Fasting/Non-fasting)	**1**[a] Non-fasting	**2**[b] Fasting	**3**[c] Fasting	**4**[c,d] Fasting	**5**[c,d,e] Non-fasting	**6**[c,d,e] Fasting	**7**[c,d,e] Fasting	**8**[c,d,e] Fasting	**9** Fasting
Week	**-6**	**-4**	**-1**	**0**	**1**	**4**	**12**	**24**	**27**
Day	**-42 to -29**	**-28**	**-7**	**1**	**8**	**29**	**85**	**169**	**190**
Visit Window		**± 3**	**± 3**	**± 0**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**
Seated BP and Pulse	X	X	X	X	X	X	X	X	X
Orthostatic BP and Pulse				X	X	X	X	X	X
12-lead ECG[k]		X							
Hepatitis Screen Panel		X							
Blood samples for Safety Laboratory Panel[l]		X		X		X	X	X	X
Blood samples for HbA1c	X			X		X	X	X	X
Blood samples for S-Creatinine (eGFR calculation)	X	X	X	X		X	X	X	X
Blood samples for FPG				X		X	X	X	X
Assess FPG for Rescue						X	X		
CCI [redacted]		X		X				X	X
CCI [redacted]				X				X	X
Pregnancy test[m]	X	X	X	X	X	X	X	X	X

Study Period	**Screening period**	**Lead-in period**		**Treatment period**					**Follow-up period**
Visit	**Enrolment**	**Start of lead-in**	**Lead-in**	**Random-ization**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**End of Treatment/ Discontinuat-ion/Rescue**	**Follow-up**
Visit Number (Fasting/Non-fasting)	**1**[a] Non-fasting	**2**[b] Fasting	**3**[c] Fasting	**4**[c,d] Fasting	**5**[c,d,e] Non-fasting	**6**[c,d,e] Fasting	**7**[c,d,e] Fasting	**8**[c,d,e] Fasting	**9** Fasting
Week	**-6**	**-4**	**-1**	**0**	**1**	**4**	**12**	**24**	**27**
Day	**-42 to -29**	**-28**	**-7**	**1**	**8**	**29**	**85**	**169**	**190**
Visit Window		**± 3**	**± 3**	**± 0**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**
Urinalysis (dipstick and spot urine collection)		X		X		X	X	X	X
Timed urine sample collection (24-hours)				X				X	
Dietary and life-style advice		X		X		X	X	X	
Dispense Glucose Meter and/or Supplies (including diaries) /Provide Instructions		X	X	X	X	X	X	X	
Review of diaries			X	X	X	X	X	X	X
Dispensation of Study Medication via IVRS/IWRS		X		X		X	X		
Return of Study Medication and accountability				X		X	X	X	
Adverse event review (AEs and SAEs)[n]	X	X	X	X	X	X	X	X	X
Hypoglycemic events review		X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X

[a] Screening procedures, indicated under Visit 1, can be completed over multiple visits, provided all procedures have been completed, with the results reviewed, prior to Visit 2.

[b] Patients must have their Visit 2 completed within 14 days following Visit 1. Visit window of ±3 for Visit 2 corresponds to the randomization visit (Visit 4). Note: The single-blind lead-in study medication and the central laboratory results from Visit 1 must have been received at the site prior to completing the entry into Visit 2.

[c] Central Laboratory samples must be collected in a fasting state (at least 8 hours of fasting prior to the study visit) except visit 5, and patients should be seen between 6 a.m. and 10 a.m. Patients must refrain from tobacco/nicotine for 12 hours and alcohol for 24 hours, respectively prior to study visits. Ensure to collect all fasting blood samples prior to the morning dose(s) of blinded study medication. Doses of study medication and other concomitant medications on the day of the visits must be taken upon completion of study visit procedures. (See CSP, Section 3.8).

[d] Double-blind treatment period visits must be scheduled according to the randomization visit date (Day 1), with a protocol-allowed visit window of ±5 days. Patients will bring their glucose meter and study supplies to the site at all visits. Any slippage in time from one visit must not accumulate to affect other visits.

[e] Randomized patients discontinuing study medication or requiring rescue should have Week 24 procedures done at the time of anti-diabetic rescue or study medication discontinuation. All patients who discontinue study medication will be asked to continue ordinary visit schedule, unless they entirely withdraw consent from the study. In patients discontinuing the study due to AE/SAE, the Investigator will follow the patients until the event has resolved or stabilized.

[f] The signature of the ICF by the prospective patient should be obtained at Visit 1. When only the Informed Consent is signed, and all other screening visit procedures are completed.

[g] eGFR value for inclusion is based on eGFR value between 45 – 59 mL/minute/1.73 m^2 at Visit 1, or Visit 2, or Visit 3.

[h] Lab values for inclusion will be based on results from Visit 2 and Visit 3. Lab values from Visit 4 will be used as baseline values for study entry.

[i] A brief physical examination should include cardiovascular (CV), lungs, abdomen, and extremities; and any organ systems pertinent to the patient's signs, symptoms, or AEs.

[j] A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, CV, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.

[k] The 12-lead ECG must be performed at Visit 2. The results from this ECG must be available, assessed, and initialed and dated by the Investigator prior to Visit 4.

[l] Includes Hematology and Clinical chemistry. Please refer to CSP, Section 5.2.1, Table 3.

[m] Only for WOCBP. Blood sample will be collected for serum βHCG test, only if urine test is positive.

[n] SAEs will be collected from the time of informed consent and AEs will be collected from the start of the placebo lead-in (Visit 2).

Screening Period (V1 to V2, 2 weeks)

At Visit 1, all potentially eligible patients will provide informed consent, undergo screening for HbA1c, eGFR level and other applicable inclusion/exclusion criteria. Visit 1 can be completed over multiple visits, provided all procedures have been completed, with the results reviewed, prior to Visit 2. Patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, should have careful monitoring of their volume status.

Placebo Lead-in Period (V2 to V4, 4 weeks)

At Visit 2 (start of lead-in), patients will be examined for HbA1c, and eGFR level, from blood sample obtained from Visit 1. If the HbA1c is ≥7.0% and ≤11% and the eGFR value is within the range of 40-65 mL/min/1.73 m^2 (MDRD-formula), patients will enter a 4-week single-blind placebo lead-in period. Blood samples will be collected for standard lab values (and eGFR level).

At Visit 2 and Visit 3, eGFR will be measured.

At Visit 4, patients who meet all of the inclusion and none of the exclusion criteria, the eGFR value within the range of 45-59 mL/min/1.73 m^2 at Visit 1, or Visit 2, or Visit 3, and the standard lab values (from Visit 2) will be randomized to the 24-week double-blind treatment period.

Table 3 Summary of the algorithm for inclusion based on HbA1c and eGFR

Visit	Algorithm
Sample obtained at Visit 1:	HbA1c ≥7.0% and ≤11%
	eGFR 40-65 mL/min/1.73 m^2, MDRD-formula
Samples obtained at Visit 1, or Visit 2, or Visit 3:	eGFR 45-59 mL/min/1.73 m^2, MDRD-formula

At randomization, patients will be stratified according to pre-enrolment anti-hyperglycemic therapy. The 5 strata are listed in Section 1.3.

Double Blind Treatment Period (V4 to V8, 24 weeks)

Following completion of the lead-in phase, eligible patients will enter the 24-week double-blind treatment phase. The dose of Oral Anti-diabetic Drugs (OADs), insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs should be kept constant throughout the 24-week double-blind treatment period.

If dose of OADs and insulin is reduced according to the investigator discretion, patient should still continue in the study with double blind treatment and the dose changes must be recorded in the appropriate sections of the electronic CRF.

Rescue Medication Due to Lack of Glycemic Control in the Treatment Period

Patients with lack of glycemic control during the 24-week treatment period may be eligible to receive open-label rescue medication in addition to their blinded treatment in order to treat ongoing hyperglycemia. Patients may receive open-label rescue medication added on to, but not as a replacement for, their current study drug regimen. Rescue medication in the study refers to any approved, appropriate anti-diabetic agent, except SGLT2-inhibitors, for which there is either initiation or upward titration, in accordance with the approved label and conventional standards of care. Open-label rescue medication is to be titrated as needed to obtain adequate glycemic control. Patients who received a first rescue medication, who subsequently fulfil lack of glycemic control criteria, may have other rescue medications added or substituted, according to Investigator judgment.

During the 24-week double-blind treatment period, all rescue decisions will be based on central laboratory FPG and confirmatory FPG results. If patients meet the protocol-specified glycemic criteria based on FPG (see Table 4 below), they will be recommended for open-label rescue medication.

Between scheduled visits, the patients will be asked to check their blood glucose if they develop symptoms suggestive of hyperglycemia. The sections and tables listed below define the lack of glycemic control criteria. Glucometers will be provided by AstraZeneca. The patients will receive instructions for the use of the glucometer according to the manufacturer's instructions. Patients will be instructed to contact the investigator if they experience a hyperglycemic event in order to schedule an extra visit for central laboratory FPG and if needed, a confirmatory, repeat FPG.

Table 4 Lack of Glycemic Control Criteria for Initiation of Open-Label Rescue Medication

Visit Label	Central Laboratory FPG
From Week 4 (Visit 6) to Week 12 (Visit 7) (excluding Week 12)	FPG >240 mg/dL (13.3 mmol/L)
From Week 12 (Visit 7) to Week 24 (Visit 8) (excluding Week 24)	FPG >200 mg/dL (11.1 mmol/L)

Patients with a central laboratory FPG value meeting the lack of glycemic control criterion at a pre-specified visit will be scheduled for a follow-up visit (within 3 - 5 days) to obtain a second central laboratory FPG value and review the patient's glucose meter readings. If the repeat central laboratory FPG value still meets the criterion, the patient will receive rescue medication.

Irrespective of study visit number, patients who meet rescue criteria in the treatment period must first complete the Week 24 visit's procedures before receipt of open-label anti-diabetic rescue medication to ensure that important study endpoint measurements are collected.

Following completion of the Week 24 "Rescue" visit, rescued patients will be administered open-label rescue medication in addition to their blinded study drug. Rescued patients will then continue in the treatment period according to their original visit schedule. Patients who received a first open-label anti-diabetic rescue medication, who subsequently fulfill lack of glycemic control criteria described in the Table 4 above, may have other rescue medications added or substituted, according to Investigator judgment, without repetition of rescue visits.

Patients with a central laboratory FPG value >200 mg/dL (11.1 mmol/L) at Week 24 (Visit 8), will not be considered as rescued for efficacy analysis.

Follow-up Period (V8 to V9, 3 weeks)

After completion of the treatment period, patients will enter a 3-week safety follow-up period without study drug. At the follow-up visit (Visit 9 (FU)) any changes in physical signs, renal function (*i.e.,* changes in eGFR), symptoms or laboratory parameters that may be related to dapagliflozin will be evaluated. Patients who discontinue study drug will remain in the study for follow-up and complete all scheduled study visits through Week 27. At the time of discontinuation the Week 24 procedures will be performed. Patients will not receive double-blind study drug during this follow-up period, but will complete all scheduled study visits and procedures.

The total planned study duration from Visit 1 to the safety follow-up (Visit 9) will be 33 weeks.

1.3 Treatment Group Assignment

The randomization codes will be computer generated by AstraZeneca R&D using the AZ Randomization system (AZRand) and loaded into the IVRS/IWRS database. Randomization codes will be generated to ensure approximate balance (1:1) between the two treatment arms (dapagliflozin 10 mg or matching placebo, once daily).

Randomization will be done via IVRS/IWRS at Visit 4. The IVRS/IWRS will allocate randomization codes sequentially through central randomization as patients become eligible for randomization.

Randomization will be stratified by pre-enrolment anti-hyperglycemic therapy. The following 5 strata will be defined:

1. Insulin-based regimen: Patients receiving insulin alone or in combination with any other anti-hyperglycemic medication

2. Metformin-based regimen: Patients receiving metformin alone or in combination with any other anti-hyperglycemic medication except insulin

3. SU-based regimen: Patients receiving a SU alone or in combination with any other anti-hyperglycemic medication except insulin and metformin

4. TZD-based regimen: Patients receiving a TZD alone or in combination with any other anti-hyperglycemic medication except insulin, metformin, or a SU

5. Other regimen: Patients receiving either any anti-hyperglycemic medication(s) not described by strata 1-4, or no background anti-hyperglycemic medication.

For each patient randomized the IVRS/IWRS will provide the investigator with a unique Kit ID number matching the treatment arm assigned to the patient. Following randomization, the first dose of study drug will be administered to the patient after completion of study visit procedures. At randomization and subsequent dispensing visit the patient should always be provided medication with the Kit ID(s) allocated by the IVRS/IWRS. If a patient receives the incorrect randomized treatment at any time during the study, the centre must immediately notify the AstraZeneca representative and IVRS/IWRS contact and this must be corrected as soon as discovered after discussing with study physician.

1.4 Sample Size Estimate

The primary endpoint is the change from baseline in HbA1c at Week 24. From post-hoc results of similar clinical studies (Study MB102029, Study D1690C00018, and Study D1690C00019) when patients meeting eGFR entry criteria like those in this current study were selected, the mean placebo-corrected change from baseline in HbA1c after 24 weeks of treatment for the current study is estimated to be -0.3% for dapagliflozin 10 mg.

Assuming a common standard deviation (SD) of 0.9% in the primary endpoint, 143 patients per treatment group with both baseline and at least one post-baseline HbA1c measurement will provide 80% power to detect a treatment difference of 0.3% in the primary endpoint at a two-sided significance level =0.05, using a two-sample t-test. Assuming that 5% of randomized patients fail to qualify for inclusion in the full analysis set due to missing baseline and/or all post-randomization values for this primary endpoint, a total of 302 randomized patients (151 per treatment group) are needed for the study.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

2.1.1 Enrolled Patients Set

The Enrolled Patients Data Set includes data collected from all patients who signed informed consent. For this study, per change to the inclusion/exclusion criteria in Amendment 3, patients can be re-enrolled a single time, but they cannot be re-randomized. Re-enrolled patients will be assigned new Ecode and will be counted only once in the Enrolled Patients Data Set.

2.1.2 Lead-in Analysis Set

For the summary of patients enrolled in the lead-in period, all patients with an E-code and who took at least one dose of lead-in medication (Placebo) will be included in the analysis set.

2.1.3 Randomized Analysis Set

For the summary of demographic and baseline characteristics, all patients assigned a randomization code by the IVRS/IWRS system will be included in the analysis set.

2.1.4 Full Analysis Set

The primary efficacy analysis will be performed on the Full Analysis Set (FAS) which will consist of all randomized patients who took at least one dose of double-blind study drug and have a non-missing baseline value and at least one post-baseline on any of the efficacy variables (HbA1c, total weight, FPG and SBP).

When the Full Analysis Set is used, patients will be presented in the treatment group to which they were randomized regardless of the treatment actually received.

2.1.5 Per Protocol (PP) Analysis Set

The PP Analysis Set is a subset of the Full Analysis Set and will consist of patients who do not deviate from the terms specified in Appendix A (important protocol deviation), which may affect the study outcome significantly and interpretation of the study results. All decisions to exclude patients from the primary data set will be made prior to the unblinding of the study.

The PP Analysis set will only be applied if the PP Analysis set has a minimum of 10% fewer patients than the Full Analysis Set due to important protocol deviations. In that case, only the primary efficacy endpoint of change from baseline in HbA1c will be analyzed using the PP Analysis set. Demographics, and baseline diabetes characteristics will be summarized using the PP Analysis set if necessary.

2.1.6 Safety Analysis Set

The Safety Analysis Data Set will consist of all patients who received at least one dose of double-blind study drug during the double-blind treatment period. The Safety Analysis Data Set will include any patient who accidentally received double-blind study drug but was not randomized in the study.

All analyses using the Safety Analysis Data Set will be presented by randomized treatment group, except in cases where information was available which indicated that a patient received a different treatment for the entire course of their participation in the double-blind treatment period of the study. In this case, the safety data for those patients will be presented by the treatment actually received. In case a patient never received the treatment as assigned by randomization, then the safety data for that patient will be presented by the first treatment received.

2.2 Blinding and Unblinding

2.2.1 Blinding

The investigator, AstraZeneca personnel, and patients will remain blinded to treatment allocation throughout the entire study period. The database used for the analysis of the double-

blind data of the study will be locked after all patients have terminated the study. In order to protect the integrity of the treatment period of the study, the patients and investigators will not have access to the individual treatment assignments until the study has completed.

Unless otherwise specified, to maintain integrity of the study, HbA1c and urinary glucose values will be masked to AZ as well as on laboratory reports to investigators during the double-blind study period. See protocol for further details.

2.2.2 Unblinding

Blinding is critical to the integrity of this clinical trial. However, in the event of a medical emergency or pregnancy, during which knowledge of the identity of the investigational product is critical to the patient's management, procedures are in place to have the blind broken for an individual patient. A separate procedure is in place for unblinding in case of expedited safety reporting to regulatory authorities.

Unmasked HbA1c and urinary glucose values will be transferred from the Central Lab between “Clean File” and “Database Lock”. Unblinding of treatment data will also occur after “Clean File” and before “Database Lock”. The locked database will be unblinded for reporting purposes.

2.3 Protocol Deviation

AstraZeneca uses ICH E3 terminology for protocol deviations, which are all important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient managements or patient assessment.

2.3.1 Protocol Deviation Monitoring

During study conduct, protocol deviations will be closely monitored and identified from two sources:

- IMPACT monitoring – deviations will be automatically derived from the database via edit checks and must be reported as a protocol deviation in IMPACT by the Site Monitor. Some protocol deviations which do not have corresponding data checks must be manually checked in the clinical database (i.e. Rave) and must be reported as a protocol deviation in IMPACT by the Site Monitor.

- Statistical programmed protocol deviation – These are deviations generated by execution of programs written using the predefined deviator descriptions in the SAP Appendix A.

The reports or information collected from IMPACT monitoring report will be reviewed and assessed periodically during study conduct by AZ/vendor study team and documented in EXCEL spreadsheet, with study id, patient id, PD collection date, PD free text term, PD coded term, PD source, major or minor criteria, and comments.

In the case of a discrepancy (e.g. statistical programming shows patient is 100% compliant with study drug but IMPACT monitoring report shows patient is non-compliant), the statistical programming from the clinical database will be considered as the definitive source.

A decision will be made prior to unblinding the study to determine which protocol deviations may significantly affect the study outcome and should be excluded completely or partially from the Per Protocol Analysis.

2.3.2 Protocol Deviation Reporting

The criteria for all major and minor protocol deviations will be provided in a separate protocol deviation document from the SAP. Protocol deviations that the study team considers to be important will be tabulated or listed in CSR.

Protocol deviations that may affect the study outcome significantly and the interpretability of the study results are defined as important protocol deviations (IPD). The criteria for important protocol deviations are given in Appendix A of the SAP.

Patients having IPD (Appendix A) will be summarized by treatment group and overall. Separate listings of all patients with important protocol deviations will also be produced.

The details of instruction of programming for IPD would be described in a separate document from the SAP.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary Efficacy Variable

The primary outcome variable will be the change from baseline in HbA1c (%).

3.2 Secondary Efficacy Variables

Secondary outcome variables will be:

- Percent change from baseline in body weight (kg).
- Change from baseline in FPG (mg/dL).
- Change from baseline in seated SBP (mmHg).

3.3 Exploratory Efficacy Variables

CCI

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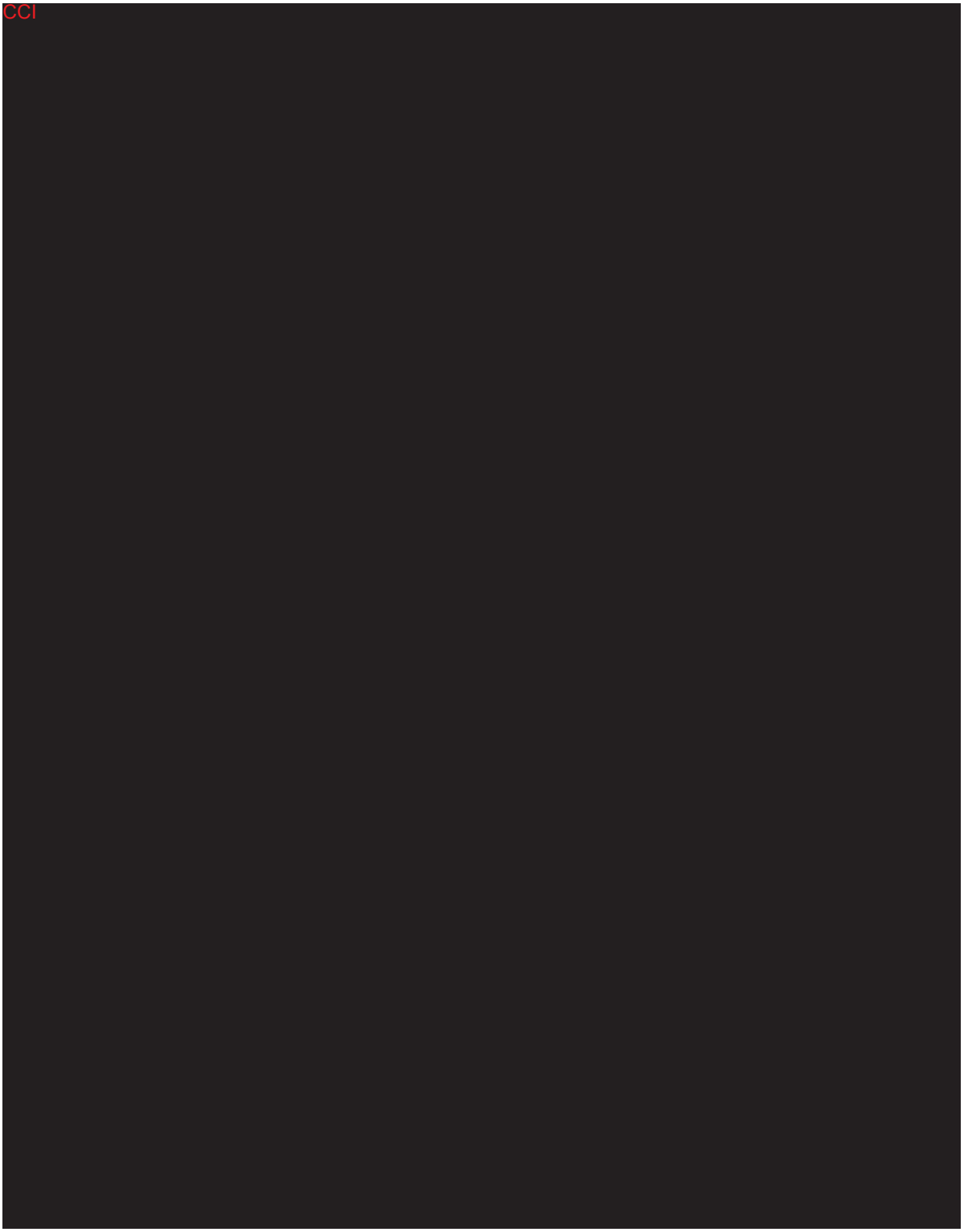

CCI

[redacted]

3.4 Safety and Tolerability Variables

No formal statistical testing of the safety and tolerability variables will be carried out. The safety and tolerability variables will be individually summarized. The safety and tolerability variables are:

- Incidence of AEs (including SAEs, other significant AEs, and AEs of special interest).
- Laboratory parameters (including marked abnormalities in clinical laboratory tests)
- eGFR
- Vital signs

4. ANALYSIS METHODS

The primary analysis of the change in HbA1c from baseline to Week 24 will be based on a mixed model repeated measures (MMRM) analysis using the FAS, and will include all available data following randomization up to and including Week 24. For all patients that are administered rescue therapy or discontinue treatment during the double-blind treatment period, only those measurements made on or prior to rescue or treatment discontinuation, (whichever occurs first) will be included in analysis.

All statistical comparisons of primary and secondary efficacy variables will be based on 2-sided test procedures with an alpha level of significance of 0.05 required to infer statistical significance, unless otherwise specified. All analyses will report nominal p-values. No other correction to the reported p-values will be made for the analysis of secondary measures. Where appropriate, interval estimates at a nominal 95% level of confidence will be presented.

An additional analysis to support primary analysis will be repeated with the primary variable (change from baseline in HbA1c using MMRM) at week 24 on the per-protocol analysis set. The sensitivity analysis in the Per Protocol Set will be applied to primary efficacy endpoints only if there will be more than 10% difference in number of patients from Full Analysis Set. Additional sensitivity analyses (including Multiple Imputation based on Retrieved Dropouts (MI-RD) and the Washout Imputation) will be performed to address the impact of missing data or initiation of rescue.

Exploratory analyses of continuous exploratory endpoints that undergo multiple assessments over the 24 week double-blind treatment period will be performed either using MMRM analyses as described for the primary analyses, or using analysis of covariance (ANCOVA), logistic regression, or descriptive summaries as warranted. Exploratory subgroup analysis will include additional covariates and interaction terms for the subgroup variables when warranted.

4.1 General Principles

The SAS System Version 9.4 will be used to perform the statistical analyses. All statistical evaluations, summaries, and tabulations will be performed by qualified personnel at Quintiles. Before unblinding of the study following clean file declaration, all decisions on the evaluability of the data for each individual patient will be made and documented and each patient will be assigned to the appropriate analysis data set.

All efficacy analyses will be based on the Full Analysis Set. The Safety Analysis Set will be used for analysis of all safety and tolerability variables.

Descriptive statistics for continuous data will include n, mean, median, standard deviation, minimum and maximum value. Descriptive data for categorical data will include n, frequency, and percentage.

The day of first dose of double-blind study medication (Day 1) will be defined as the reference start date for the randomized treatment period and will appear in the listings where an assessment date or event date appears when appropriate.

- 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).

A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses. The window definitions as outlined in Section 4.3.1 will be used for the efficacy and safety analyses.

4.1.1 Baseline Values

For all efficacy variables summarized for the FAS, the baseline value will be the last non-missing value on or prior to the date of the first dose of double-blind study drug. For the sensitivity analyses on primary efficacy variable when summarized for the Randomized Analysis Set, if a patient is randomized but is not administered double-blind study medication then the baseline value will be the last non-missing value on or prior to the randomization date.

The baseline value of each safety laboratory test or ECGs or physical exam endpoint is defined as the last assessment (either numerical or character value) on or prior to the date of the first dose of double-blind study drug.

4.1.2 Change and Percent Change from Baseline

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

$$Change = Measurement\ at\ Week\ t\ - Baseline$$

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

$$Percent\ change = \frac{Measurement\ at\ Week\ t\ - Baseline}{\text{Baseline}} \times 100$$

The "Week t" to which a measurement belongs is determined using the conventions described in Section 4.3.

4.1.3 Derivation of Efficacy Variable at Rescue/ Premature Discontinuation

In efficacy analyses, the glycemic parameters will only include measurements obtained prior to or on the date of rescue medication administration or discontinuation of double-blind medication (whichever is earlier). An exception would be in sensitivity analysis, where the analysis is performed on data regardless of rescue (see more details in Section 4.2.6.2).

For secondary efficacy variables of body weight (kg), seated SBP (mmHg) and remaining exploratory variables, measurements after rescue medication will not be excluded from the analyses.

Patients not completing the treatment period should have all Week 24 visit procedures done at the time of study discontinuation or rescue.

Patients who meet the pre-specified rescue criteria, at the specified visit described in Table 4, will be scheduled for a follow-up visit (within 3-5 days) to obtain a confirmatory central lab FPG value. If the confirmatory FPG value still meets the criteria, the patient will be rescued.

4.1.4 Analysis of Covariance

4.1.4.1 ANCOVA Model for Change from Baseline

Unless otherwise specified, when an analysis of covariance (ANCOVA) model is used to analyze a continuous variable, the model will include the fixed main effects of treatment group, anti-diabetic treatment strata at randomization, and the baseline measurement as a covariate.

The ANCOVA will present least squares (LS) mean estimates and 2-sided 95% confidence intervals (CIs) for mean changes from baseline by treatment group and differences in LS mean estimates, the corresponding 2-sided 95% Cis and nominal p-values.

4.1.4.2 ANCOVA Model for Percent Change from Baseline

Unless otherwise specified, for analyses of parameters in terms of percent change from baseline at Week t, ANCOVA analysis will be performed on the difference between natural logarithmically transformed value at the end of treatment and at baseline [$\log_e$(post) – $\log_e$(baseline)], and will include terms for treatment, the log-transformed baseline value and anti-diabetic treatment strata at randomization.

Least squares estimates and differences and the corresponding 95% confidence intervals obtained from the model output will be used to generate estimates of (geometric) mean percent change. Where applicable, the t-statistic corresponding to the Type III sums of squares for the differences in the least squares means will be used to obtain p-values for treatment group comparisons.

Table 5 details the formulae that will be used to transform back the results from the ANCOVA model to obtain the values reported in the tables.

4.1.5 Last Observation Carried Forward (LOCF)

Unless otherwise specified, when an analysis of covariance (ANCOVA) model is used to analyze a continuous variable, analyses will be based on measurements at the time point Week 24, if no measurement is available at that time point Week 24 (patient has discontinued before Week 24, or measurement not taken at Week 24 though patient was not discontinued), the last available post-baseline measurement will be carried forward (LOCF). For glycemic parameters for patients who started rescue medication or discontinued double-blind medication prior to Week 24, their last post-baseline measurement taken prior to or on the date of the first dose of rescue medication or the discontinuation date (whichever is earlier) will be used.

4.1.6 Longitudinal Repeated Measures Analysis

4.1.6.1 Longitudinal Repeated Measures Analysis for Change from Baseline

For changes from baseline to Week 24 in all efficacy parameters (e.g. HbA1c, FPG, and seated SBP etc.) and exploratory analysis on continuous endpoints (e.g. eGFR, CCI [redacted] etc.), analyses will be based on a longitudinal repeated measures

(MMRM) analysis using "direct likelihood". The SAS procedure PROC MIXED will be used. The preferred model for this analysis will include the fixed categorical effects of treatment, week, randomization stratification factor (i.e. anti-diabetic treatment strata), and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.

An unstructured covariance structure will be used to model the within-patient error. The Kenward-Roger approximation (Kenward and Roger, 1997) will be used to estimate denominator degrees of freedom.

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

- The first backup model is the same as the preferred model but the Kenward-Roger method will be replaced by Satterthwaite approximation.
- 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 mixed model will provide least-squares mean estimates, standard errors and 2-sided 95% confidence intervals within each treatment group. The differences in least-squares means, 2-sided 95% confidence intervals and p-value of the differences in week 24 visit estimates between dapagliflozin and placebo will be presented as well.

4.1.6.2 Longitudinal Repeated Measures Analysis for Percent Change from Baseline

Unless otherwise specified, for all percent changes from baseline to Week 24 in efficacy parameters (e.g. percent change from baseline in body weight (kg), percent change from baseline in CCI [redacted] analyses will use the longitudinal repeated measures analysis; as the difference between the natural logarithmically transformed Week 24 and baseline values.

The difference between the natural logarithm of Week 24 values and the natural logarithm of baseline values will be used as response variable for this analysis model. The preferred model will include the fixed categorical effects of treatment, week, randomization stratification factor (i.e. anti-diabetic treatment strata), and treatment-by-week interaction, as well as the continuous fixed covariates of natural logarithm of baseline measurement and natural logarithm of baseline measurement-by-week interaction.

Exponentiation of estimates based on differences on a natural logarithmic scale will be performed prior to reporting, and geometric values (e.g., estimates, standard errors, differences and standard errors, and 95% confidence limits) will be converted to percentages prior to reporting, and reported on a percentage scale. See Table 5 for more details.

Table 5 Formulae Used to Transform Back the Results from ANCOVA Model or Longitudinal Model onto the Original Scale.

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

Table 5 Formulae Used to Transform Back the Results from ANCOVA Model or Longitudinal Model onto the Original Scale.

Quantity	***Computation method***
Adjusted geometric mean of the Week *t* to baseline ratio achieved with each dapagliflozin *treatment arm* relative to that achieved with C*ontrol*, expressed as a percent difference. Please note that for the SAS output, a shorter text will be used: Adjusted GM of Week *t*/Baseline for each dapagliflozin *treatment arm* relative to *Control*, in % difference.	100 x (((adjusted mean percent change for dapagliflozin *treatment arm* +100)/(adjusted mean percent change for *Control* +100)) – 1) – or, equivalently – 100 x (exp(difference in adjusted mean change from baseline between dapagliflozin *treatment arm* and *Control* in natural logarithm) – 1)

4.1.7 Handling of Dropouts or Missing Data

The primary estimand will be the treatment difference at Week 24 if all subjects had remained in the trial and received treatment as planned without rescue medication. In order to address the impact of missing data, initiation of rescue therapy, and premature treatment discontinuation on the primary efficacy analysis, the analysis of the primary efficacy endpoint will be repeated in sensitivity analyses.

For the assessment of efficacy, interpretation of results in the presence of missing data depends on the missing data mechanism assumptions as well as on the use of data collected after initiation of rescue therapy or premature study treatment discontinuation in the analysis. In this study, the primary efficacy analysis is performed using an MMRM which assumes MAR, and based on data collected up to initiation of rescue or premature study treatment discontinuation, whichever occurs first.

Two additional methods of sensitivity analyses will be performed. These are Multiple Imputation based on Retrieved Dropouts (MI-RD) and Washout Imputation based on Randomized Set.

In multiple imputation a common (fixed) seed value of 29653, and 1000 simulations will be performed. The detailed analysis plan and implementation of these methods are described in Sections 4.1.7.1 and 4.1.7.2 to, respectively.

To address the impact of missing data on primary efficacy analysis, the amount of missing data, the distribution of missing data among treatment groups, and the reasons for missing data will be examined. The proportion of patients with missing HbA1c assessments will be summarized by treatment group, scheduled time point during the double-blind treatment period, and categories of missing causes if applicable. In addition, spaghetti plots of mean HbA1c profiles over time will be provided for each treatment to assess the patterns of missing HbA1c assessments, with patients grouped according to the time of the last assessment prior to rescue or discontinuation.

4.1.7.1 Multiple Imputation based on Retrieved Drop-outs (MI-RD)

In MI-RD, all patients in the randomized set who have a baseline assessment (regardless of rescue or treatment discontinuation) will be included in the analysis. Based on status of whether the patients have early treatment discontinuation and whether the assessment is available at Week 24, the population will be categorized as 4 subpopulations described in Table 6.

The main steps of the implementation of MI-RD are described below.

Step 1: Impute missing data for patients without HbA1c at Week 24 using a regression model imputation based on data from patients who discontinued treatment but had HbA1c assessment at Week 24 within that treatment group. The HbA1c baseline will be used as explanatory variable for imputation. If, for each (protocol-defined) visit where there is at least 1 patient with a last on-treatment assessment and is missing a Week 24 HbA1c value, there are (at that same visit) sufficient numbers of patients with a last on-treatment assessment that subsequently discontinued treatment but have a Week 24 HbA1c value, then the missing Week 24 HbA1c values will be imputed from the non-missing Week 24 HbA1c values by "last on-treatment visit" within each treatment group. Otherwise, if there are sufficient numbers of patients that discontinued treatment but have a Week 24 HbA1c value (regardless of last protocol-defined visit "on-treatment") then missing Week 24 HbA1c values will be imputed from the patients that have discontinued treatment but have Week 24 HbA1c values within each treatment group. The imputation population and process are described in Table 6. Imputation will be done within each treatment group.

Step 2: Analyze the multiple imputed HbA1c change from baseline at Week 24 using ANCOVA model. Combine estimates obtained from multiple imputed datasets based on Rubin's combination rules (Little R., Rubin D.B. 2002).

The MI-RD approach requires a sufficient number of patients who discontinued treatment but had HbA1c assessment at Week 24 in each treatment. If there is not a sufficient number of patients to do the analysis, then this approach will not be implemented.

Table 6 Patterns for Imputation of Missing HbA1c data at Week 24 with the MI-RD approach

Subpopulations (patterns) considered in the imputation process	Imputation at Week 24
Subpopulation 1: Patients who were on treatment with HbA1c at Week 24.	No action
Subpopulation 2: Patients who discontinued treatment by Week 24 but had HbA1c assessments at Week 24.	No action

Table 6 Patterns for Imputation of Missing HbA1c data at Week 24 with the MI-RD approach

Subpopulations (patterns) considered in the imputation process	Imputation at Week 24
Subpopulation 3: Patients who discontinued treatment by Week 24 without HbA1c assessments at Week 24.	Use data from Subpopulation 2 patients to estimate imputation model.
Subpopulation 4: Patients who did not discontinue treatment prematurely but without HbA1c assessments at Week 24 (patients lost to follow-up).	Use data from Subpopulation 2 patients to estimate imputation model.

4.1.7.2 Washout Imputation

In washout-imputation, all patients in the randomized set who have a baseline assessment (regardless of rescue or treatment discontinuation) will be included in the analysis. This imputation method will only impute the time point at Week 24 for the active treatment using multiple imputation regression with randomization strata and baseline HbA1c as the predictors. This approach ignores any post-baseline changes in the HbA1c values when predicting missing Week 24 values and will impute all patients similar to an average placebo patient. ANCOVA will be used as the analysis method.

The main steps of the implementation of the washout imputation are described below.

Step 1: Impute Week 24 missing data for patients in the active treatment using regression model multiple imputation based on data from the placebo arm. For patients in placebo arm missing data at any time point will be imputed assuming MAR mechanism. The variables used as explanatory variables for imputation include Randomization strata and HbA1c baseline.

Step 2: Analyze the multiple imputed data at Week 24 using ANCOVA model. Combine estimates obtained from multiple imputed datasets based on Rubin's combination rules (Little R., Rubin D.B. 2002).

4.1.8 Summaries of Continuous Endpoints

Descriptive statistics will be used to present efficacy and safety variables. For continuous variables, n, mean, standard deviation (or standard error), median, minimum, and maximum will be presented by visit when applicable.

The changes from baseline will be summarized for relevant efficacy and safety parameters and will include 95% CIs for means. The percent changes from baseline will be summarized for

selected lab parameters and will include 95% CIs for means. Summaries for continuous endpoints will also include quartiles.

4.1.9 Proportion of Patients with Pre-Defined Characteristics

Exploratory analyses of variables that represent proportions of patients (e.g. proportions of patients achieving response in CCI [redacted] at Week 24 LOCF) will be performed using the logistic regression model when there are at least 5 responders in each treatment group. For proportion of responders CCI [redacted], estimates, confidence intervals, and tests will be obtained using logistic regression model with adjustment for baseline variable(s) and pooled randomization strata to accommodate composite endpoints (e.g, adjustment for baseline CCI [redacted] and pooled randomization strata).

For analysis using the logistic regression model, the pooled randomization strata will be used as the adjustment factor. Patients with randomization strata in Metformin-based regimen, SU-based regimen, TZD-based regimen, and Other regimen will be pooled together as in one strata group called as "oral antidiabetic medications". For the analysis on the proportion of patients initiating insulin therapy in patients not on insulin at the start of the study, since all patients would be in strata of "oral antidiabetic medications", strata will be excluded in model in this analysis.

The estimated odds ratio of dapagliflozin treatment group to the placebo group will be displayed along with standard error and the 95% confidence intervals. P-values will be calculated if applicable. Raw proportions will also be displayed by treatment group. When there are less than 5 responders in each treatment group, the unadjusted (and difference) proportions, exact 95% confidence interval, and p-values from the Fisher's exact test (when applicable) will be provided. Although p-values will be generated for exploratory endpoints, statistical significance will not be inferred and claims will not be made.

4.1.10 Summaries of Shifts from Baseline in Categorical Variables

Changes from baseline in certain categorical variables will be summarized using shift tables. Frequencies and percents of patients within each treatment group will be generated for levels of cross-classifications of baseline and the on-treatment value of the variable. The on-treatment value can be either the value at a certain time point, (for example, laboratory tests) or the minimum/maximum value in the direction of toxicity, which has been observed during a study period. Treatment group differences will not be assessed in summaries of shifts.

4.1.11 Kaplan-Meier Curve and Estimates for Time-To-Event Analyses

Kaplan-Meier plots (Kaplan EL and Meier P 1958) will be used to generate product-limit estimates of probabilities for CCI [redacted] by treatment for the 24-week double-blind period. Estimated probabilities will be displayed by treatment group as "overlay curves". Probabilities will be connected to form a "survival curve" across rescue times and the last rescue will be carried-forward to Week 24. Additionally, a summary 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 (Greenwood M 1926)) of patients 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. Unless otherwise specified, the plot will be presented only when there are at least 5 events in one treatment group.

4.1.12 eGFR

eGFR is calculated according to the MDRD formula): GFR (mL/min/1.73m^2) = 175 x (standardized sCr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if Black)] [Note: sCr reported in mg/dL].

4.2 Analysis Methods

4.2.1 Patient Disposition

All patients enrolled (who signed informed consent) will be summarized. The disposition of patients for the lead-in period, the double-blind treatment period and the whole study which include follow-up period will be summarized.

The summary of status in the lead-in period will include all patients receiving at least one dose of study drug (placebo) during the lead-in period. The summary of status in the double-blind treatment period will include all patients in Randomized Data Set. The number and percent of patients who entered, completed and discontinued, with the reasons for discontinuation will be summarized for each period (lead-in, double-blind treatment and the whole study which includes follow-up period). Summaries of double-blind and the whole study which includes follow-up period will be made by treatment group and overall.

A listing of patients who discontinued from the lead-in period and from the double-blind treatment period will be provided.

Patients enrolled, randomized, and treated will be summarized by country and study site.

4.2.2 Demographics and 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 Data Set.

Demographic and baseline characteristics are listed in Table 7. Diabetes related baseline characteristics are listed in Table 8. Common renal function baseline characteristics are listed in Table 9.

Table 7 Demographic and baseline characteristics

Characteristic	Summarized as	Categories
Gender	Categorical	Male, Female
Age	Categorical and Continuous	<65 yrs ≥65 yrs
Female Age	Categorical	≤50 yrs >50 yrs
Race	Categorical	White Black or African American Asian Native Hawaiian or Other Pacific Islander American Indian or Alaska Native Other
Ethnicity	Categorical	Hispanic or Latino Not Hispanic or Latino
Body weight	Continuous	--
CCI	Continuous	--
Body Mass Index	Categorical and Continuous	<25 kg/m^2 ≥25 kg/m^2 ≥27 kg/m^2 ≥30 kg/m^2
Geographic Region	Categorical	As defined in Appendix B

Table 8 Diabetes-Related Baseline Characteristics

Characteristic	Summarized as	Categories
Duration of type 2 diabetes	Categorical and Continuous	<3 yrs ≥3 and ≤10 yrs >10 yrs
HbA1c	Categorical and Continuous	<8% ≥8-<9% ≥9-<10% ≥10%

Table 8 Diabetes-Related Baseline Characteristics

Characteristic	Summarized as	Categories
FPG	Categorical and Continuous	<110 mg/dL ⩾110 - <150 mg/dL ⩾150 - <200 mg/dL ⩾200 - <240 mg/dL ⩾240 - <300 mg/dL ⩾300 mg/dL
pre-enrolment anti-hyperglycemic therapy	Categorical	Insulin-based regimen SU-based regimen TZD-based regimen Metformin-based regimen other regimen

Table 9 Baseline Renal Function Characteristics

Characteristic	Summarized as	Categories
eGFR (MDRD)	Categorical and Continuous	<30 mL/min/1.73 m^2 ⩾30 and <45 mL/min/1.73 m^2 ⩾45 and <60 mL/min/1.73 m^2 ⩾60 and < 90 mL/min/1.73 m^2 ⩾90 mL/min/1.73 m^2
CCI	[redacted]	[redacted]

All summaries of continuous characteristics will be based on non-missing observations. Summary statistics including mean, median, SD, the first and third quartiles will be calculated. For categorical characteristics, percents will be calculated out of the total number of patients in the data set, overall and by treatment group (ie, each denominator includes the number of patients with missing/unknown values for the endpoint).

Duration of Type 2 diabetes is calculated as the number of years from Type 2 diabetes diagnosis date to informed consent date:

(consent date - diagnosis date + 1) / 365.25.

The duration of diabetes will be included in the baseline diabetes characteristics listing. If the date Type 2 diabetes was diagnosed is partially missing, the following rules will take effect:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
- Missing day and month, but year is present: the day and month will be imputed as 30 June of the year.
- Missing year, but day and month are present: No imputations will occur, and the patient will be excluded from all summaries related to duration of Type 2 diabetes.
- Missing day, month and year: No imputations will occur, and the patient will be excluded from all summaries related to duration of Type 2 diabetes.

If any such imputed date falls after the consent date, then the diagnosis date will be taken as equal to the consent date.

Demographic and baseline diabetes characteristics will be presented in listings for each patient in the Randomized analysis set.

4.2.3 Specific and General Disease Histories

The numbers and percents of patients with diabetes history, general medical history findings and surgical history will be summarized by body system for each treatment group and overall using the Randomized Analysis Set.

For these displays, percents will be calculated out of the total number of patients in the data set, overall and by treatment group (i.e., each denominator includes the number of patients with missing/unknown values for the endpoint).

The specific disease history and general medical history will be presented in listings for each patient in the Randomized Analysis Set.

4.2.4 Current and Concomitant Medications

Current and concomitant medications will be summarized using the Safety analysis set by drug class (anatomic class and therapeutic class), generic drug name and treatment group, as defined by the AstraZeneca Drug Dictionary most current at time of database lock. A summary will be produced for each of the following:

- all current medication
- all concomitant medication
- all concomitant 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 double-blind 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 during the double-blind treatment period is defined a medication with either

- a recorded medication start date falling within the double-blind treatment period, or
- a recorded medication start date prior to the first day of study medication during the double-blind treatment period without any recorded medication stop date prior to the start of the double-blind treatment period.

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

Missing and partial date handling of start and stop dates of previous, current and concomitant medications, is described in Section 4.3.6.

4.2.5 Extent of Exposures

4.2.5.1 Study Therapy

Extent of exposure is defined as the number of days between the start and the end dates of study therapy, where the start date of study therapy is the date of the first dose of investigative or comparator treatment, and the end date of study therapy is the last known dose of investigative or comparator treatment during the double-blind randomized treatment period, ie,

Extent of exposure=Last dosing date - First dosing date + 1.

Extent of exposure to the investigational product will be summarized using Safety analysis set for the double-blind treatment period regardless of rescue and prior to rescue respectively, presenting the numbers and percents of patients with an extent of exposure within the following day ranges by treatment group: 1 to 14, 15 to 28, 29 to 42, 43 to 56, 57 to 84, 85 to 112, 113 to 168, and ≥169 days. Also the mean, SD, median and range of extent of exposure to study medication will be presented by treatment group.

Extent of exposure for the investigational product during the double-blind treatment period will be summarized and listed by patient. Additionally, a listing of randomization scheme and a listing of patients by batch number of investigational product will be produced.

Also, rescue medication usage (number of patients taking rescue medication or insulin) will be summarized by treatment group based on CRF records. A by patient listing for rescue medication usage will be presented for all rescued patients during double-blind treatment period.

4.2.5.2 Treatment Compliance

Percent treatment compliance is calculated during the double-blind treatment period for the blinded study medication. Percent compliance is defined as the number of tablets taken, divided by the number of tablets that should have been taken. A patient is considered compliant if percent compliance is between 80% and 120%, inclusive. The number of tablets that should have been taken is calculated as (date of the last investigational dose - date of 1st investigational dose during randomized treatment period + 1), times the prescribed daily dose. Total number of tablets taken is the difference between total number of tablets dispensed minus total number of tablets returned over the entire randomized treatment period. All dates and tablets counts data are to be taken from the "Drug Accountability" or DA module in CRF.

The number and percent of patients compliant with double-blind study drug during the double-blind treatment period will be summarized for the safety analysis set.

4.2.6 Efficacy Variables

4.2.6.1 Primary Efficacy Variable

The primary objective of this study is to compare the mean change from baseline in HbA1c between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes and CKD stage 3A. The primary estimand will be the treatment difference at Week 24 if all patients had remained in the trial and received treatment as planned without rescue medication. The analysis of the primary estimand will include all available data up to Week 24 or premature discontinuation of randomized treatment, whichever occurs first.

The null and alternative hypotheses of interest are:

H_0: $\mu_s = \mu_p$ VS H_a: $\mu_s \neq \mu_p$,

Where μ_s and μ_p are mean change from baseline to week 24 in HbA1c for study medication dapagliflozin and placebo groups respectively.

For rescued patients, measurements obtained after rescued medication or rescued insulin will be excluded. For patients discontinuing double-blind medication, measurements obtained after discontinuation will be excluded.

The primary analysis for the change in HbA1c from baseline at Week 24 will be based on longitudinal repeated measures analysis as described in Section 4.1.6.1. For all patients that are administered rescue therapy or discontinue treatment during the double-blind treatment period, only those measurements made on or prior to rescue or treatment discontinuation, (whichever occurs first) the will be included in analysis. For the primary efficacy analysis, the additional 3-way interaction term Baseline*Week*Treatment will be used as a model check to assess if there is statistically significant treatment effect across visits which differs in dependency on baseline values.

Point estimates and 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between dapagliflozin 10 mg treatment group and the placebo treatment group will be calculated. P-value will be calculated to compare the treatment effect in the dapagliflozin 10 mg treatment group to that in the placebo treatment group.

4.2.6.2 Sensitivity Analysis

To assess the robustness of the primary efficacy analysis, and to compare the results with previous studies, the sensitivity analyses on the primary efficacy endpoints will be carried out using the following approaches:

- Repeat of the primary analyses for the Per Protocol Set (if warranted) which is a subset of the Full Analysis Set and will consist of patients who do not deviate from the terms of the protocol, utilizing the longitudinal repeated measures methodology described in Section 4.1.6.1, only include measurements prior to rescue and treatment discontinuation.

  Note the sensitivity analysis using the Per Protocol Set will be applied to primary efficacy endpoints only if there the Per Protocol Set has a minimum of 10% fewer patients for any treatment group than the Full Analysis Set.

- Repeat of the primary analyses for the Full Analysis Set who have a baseline assessment and any post-baseline double-blind treatment period HbA1c assessment utilizing longitudinal repeated measures methodology described in Section 4.1.6.1, with adjustment for baseline eGFR and baseline eGFR-by-week interaction, in addition to adjustment for baseline HbA1c and baseline HbA1c-by-week interaction, only include measurements prior to rescue and treatment discontinuation.

- Repeat of the primary analyses for the Randomized Set who have a baseline assessment regardless of rescue or treatment discontinuation utilizing ANCOVA at Week 24 within the framework of MI-RD imputation described in Section 4.1.7.3.

- Repeat of the primary analyses for the Randomized Set who have a baseline assessment regardless of rescue or treatment discontinuation utilizing ANCOVA at Week 24 within the framework of Washout-imputation described in Section 4.1.7.4.

Summaries and analyses supporting the primary efficacy objective are:

AstraZeneca

Table 10 Summary of Analysis to meet primary efficacy objective of HbA1c

Analysis type	Estimand	Missing Data Assumption	Imputation Method	Analysis set
Repeated measures mixed model of ΔHbA1c to Week 24 (prior to rescue and treatment discontinuation)[a]	Difference in outcome improvement at Week 24 without rescue and without treatment discontinuation.	MAR	No imputation	FAS[a]
Repeated measures mixed model of ΔHbA1c to Week 24 (prior to rescue and treatment discontinuation)[b]	Difference in outcome improvement at Week 24 without rescue and without treatment discontinuation. For PP analysis set only.	MAR	No imputation	PP[b]
Repeated Measures mixed model of ΔHbA1c to Week 24 with adjustment for baseline eGFR in addition to adjustment for baseline HbA1c (prior to rescue and treatment discontinuation)	Difference in outcome improvement at Week 24 without rescue and without treatment discontinuation.	MAR	No imputation	FAS
ANCOVA of ΔHbA1c to Week 24 from MI-RD imputation	Difference in outcome improvement at Week 24 regardless of rescue or treatment discontinuation.	MNAR	Observed and Imputed values	RAND
ANCOVA of ΔHbA1c to Week 24 from washout imputation	Difference in outcome improvement at Week 24 regardless of rescue or treatment discontinuation.	MNAR	Observed and Imputed values	RAND

ΔHbA1c=change from baseline in HbA1c; PP=Per Protocol; FAS = Full analysis set

[a] The primary analysis

[b] The sensitivity analysis on PP will be applied to primary efficacy endpoint only if there will be more than 10% difference in number of patients from FAS

4.2.6.3 Secondary Efficacy Variables

The secondary endpoints, i.e, percent change from baseline in total body weight (using logarithmic transformation) at Week 24, change from baseline in FPG at Week 24, change from baseline in seated SBP at Week 24, will be analyzed using a longitudinal repeated measures analysis, similar to the one used for the primary analysis of the primary endpoint.

Summaries and analyses supporting the secondary efficacy objectives are:

Table 11 Summary of Analyses to Meet Secondary Efficacy Objectives

Analysis type	LOCF or Observed values	Analysis set
Repeated measures mixed model of percent change from baseline to Week 24 in body weight (kg) (prior to treatment discontinuation)	Observed values	FAS
Repeated measures mixed model of change from baseline to Week 24 in FPG (mg/dL (prior to rescue and treatment discontinuation)	Observed values	FAS
Repeated measures mixed model of change from baseline to Week 24 in seated SBP (mmHg) (prior to treatment discontinuation)	Observed values	FAS

LOCF = Last Observation carried Forward; FAS = Full analysis set

4.2.6.4 Sequential Testing Procedure

A sequential testing procedure will be employed among the primary endpoint and secondary endpoints in order to control the type I error rate at the 0.05 level. The tests for the secondary efficacy endpoints will be performed only if the test for the primary endpoint is significant, in which case the secondary endpoints will be tested in the order that they appear in the Table 11. Statistical tests will be only performed for a given secondary endpoint if all previous sequential tests for that comparison between dapagliflozin and placebo are also significant. Otherwise, the testing procedure will stop at the secondary endpoint that does not reach statistical significance. If either the testing procedure is stopped or superiority to placebo is not demonstrated, then nominal p-values will be provided.

4.2.6.5 Exploratory Efficacy Variable

CCI

Table 12 lists the summary of exploratory analyses on continuous endpoints.

Table 12 Summary of analyses to exploratory analysis on continuous endpoints

Analysis Type	LOCF or observed values	Analysis Set
CCI		

ANCOVA = Analysis of Covariance; LOCF = Last Observation carried Forward; FAS = Full analysis set

Exploratory analyses of variables that represent proportions of patients will be performed using the methodology as described in Section 4.1.9.

Table 13 lists the summary of exploratory proportion analyses.

Table 13 Summary of exploratory analysis on categorical endpoints

Analysis Type	LOCF or observed values	Analysis Set
CCI		

Table 13 Summary of exploratory analysis on categorical endpoints

Analysis Type	LOCF or observed values	Analysis Set
CCI		

Table 13 Summary of exploratory analysis on categorical endpoints

Analysis Type	LOCF or observed values	Analysis Set
CCI		

CCI

4.2.6.6 Subgroup Analysis for Efficacy Variables

CCI

CCI

[redacted]

Table 14 Contrast Coefficients for the Example Gender-by-treatment Interaction

Gender	Male	Male	Female	Female
Treatment group	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
Contrast coefficient	-1	1	1	-1

Table 15 lists the subgroup variables with the efficacy endpoints.

Subgroup analysis for other efficacy and safety variables will be conducted as deemed appropriate and necessary.

Table 15 Subgroup analysis for the efficacy variables

Analysis endpoints	Grouping Variable	Category	Analysis set used

CCI

[redacted]

Table 15 Subgroup analysis for the efficacy variables

Analysis endpoints	Grouping Variable	Category	Analysis set used
CCI			

4.2.7 Safety Variables

The Safety Analysis Set will be used for all safety analyses, including all data after rescue during the double-blind treatment period. Sensitivity analyses on data collected prior to rescue during the double-blind treatment period will be performed for selected Adverse Events (AEs) as described in multiple sub-sections under Section 4.2.7.1.

Safety analyses will be conducted on the double-blind treatment period and follow-up period.

AEs within 4 days or SAEs within 30 days post last double-blind study medication, which are considered in the double-blind treatment period, will not be counted as AEs or SAEs during the follow-up period.

Unless otherwise specified, the safety analyses of changes from baseline to a specific time point in safety variables (e.g., laboratory parameters and vital signs) will only include patients from the Safety Analysis Set who have data available for both the baseline and the time point under consideration.

Safety data that collected before randomization will not contribute to summaries but will be listed.

4.2.7.1 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). All adverse events will be coded using the latest available version of MedDRA by the database lock.

Unless otherwise specified, no statistical tests will be performed to compare AE rates between treatment groups. This policy was adopted to recognize the lack of power and the potential for misleading interpretation based on repeated statistical tests which increase the family wise Type I error level.

Counting rules for adverse events are described in Section 4.3.8.

In summaries by system organ class (SOC) and preferred term (PT), AEs will be sorted by decreasing frequency of each PT and SOC, within SOC, according to the Dapagliflozin 10 mg group. In summaries by PT, AEs will be sorted by decreasing frequency of PT according to the Dapagliflozin 10 mg group.

Missing AE dates will be imputed as defined in Section 4.3.3.

Separate pages to capture events of hypoglycemia and to capture all potential events of DKA are contained within the CRF. Discontinuation due to hypoglycemia would not be reported on an AE CRF page unless the event fulfilled criteria for an SAE in which case an SAE form would be completed. Hypoglycemia and DKA events that are reported as SAEs will be included in all summaries of AEs or SAEs (see Section 4.2.7.1.1). Separate summaries will be

provided including hypoglycemia events reported on the hypoglycemia CRF pages (see Section 4.2.7.1.6 Adverse Events of Special Interest).

4.2.7.1.1 All Adverse Events

All adverse events (serious and non-serious) with onset during the double-blind treatment period will be summarized by system organ class, preferred term and treatment group, for both the primary and sensitivity safety analyses.

The patient incidence of Related AEs, Deaths, SAEs and AEs Leading to Discontinuation of Study Medication (DAEs) will be summarized. Hypoglycemic and DKA events that are reported on separate eCRF pages will be summarized separately.

In addition, following summaries will be provided for the double-blind treatment period. These summaries will exclude hypoglycemic AEs:

- Proportion of patients with adverse events in subgroups of patients defined by age category (< 65 and ≥65 yrs), gender, race and female age category (≤50 and >50 yrs).
- Most common adverse events by preferred term and treatment group (reported by ≥2% and ≥5% of patients in any treatment group).
- Adverse events by system organ class, preferred term, intensity and treatment group.
- Adverse events related to study medication by system organ class, preferred term and treatment group.

All AEs occurring during the study (including the placebo lead-in period, double-blind treatment and the follow-up period) will be listed.

4.2.7.1.2 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 listing of all deaths that occur during the study will be produced.

4.2.7.1.3 Serious Adverse Events

SAEs (including hypoglycemic and DKA events) with an onset from Day 1 of double-blind treatment up to and including 30 days after the last dose date in the double-blind treatment period will be considered as occurring during the double-blind treatment period.

SAEs (including hypoglycemic and DKA events) occurring during the double-blind treatment period will be summarized by SOC, PT and treatment group. In addition, the proportion of patients 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) that occurred during the study.

4.2.7.1.4 Related Adverse Events

The patient incidence of related AEs will be presented by SOC, PT and treatment group.

4.2.7.1.5 Adverse Events Leading to Discontinuation (DAE)

AEs with an onset during the double-blind treatment period reported with an action taken of discontinuation of study medication will be summarized by SOC, PT and treatment group.

When summarizing AEs leading to discontinuation, no upper cutoff day windows (i.e. 4 days and 30 days from last dosing date in double-blind treatment period for AEs and SAEs respectively) are applied. For double-blind period analyses, the only upper cutoff date is the last date of the double-blind treatment period.

In addition, a patient listing of discontinuation due to AEs will be provided, displaying all events that led to discontinuation that occurred during the study.

4.2.7.1.6 Adverse Events of Special Interest

Separate summaries will be provided for the following adverse events of special interest. To identify each type of adverse event of special interest in this section, a list of preferred terms will be selected, reviewed and finalized prior to the database lock and unblinding of the database.

- Genital Infection
- Urinary-tract Infection
- Volume depletion (including hypotension, dehydration, and hypovolemia)
- Renal Impairment/Renal Failure
- Bone Fractures

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

4.2.7.1.6.1 Hypoglycemia

Separate pages to capture events of hypoglycemia are contained within the CRF.

Hypoglycemic events with an onset from Day 1 of the double-blind treatment period up to and including 4 days (30 days for SAE) after the last dose date in the double-blind treatment period will be considered as occurring during the double-blind treatment period. The

proportion of patients with hypoglycemic events will be tabulated by treatment group in the double-blind treatment period. Both primary and sensitivity safety analyses will be performed. Hypoglycemic events will be categorized using the following classes:

- Major episodes of hypoglycemia - defined as symptomatic episodes requiring external (3rd party) assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose value <3 mmol/L (<54 mg/dL), and prompt recovery after glucose or glucagon administration,

- Minor episodes of hypoglycemia - defined as either a symptomatic episode with a capillary or plasma glucose measurement below 3.5 mmol/L (63 mg/dL) regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement below 3.5 mmol/L (63 mg/dL), that does not qualify as a major episode,

- Other episodes of hypoglycemia - defined as episodes reported by the investigator that are suggestive of hypoglycemia but do not meet the above criteria.

When summarizing hypoglycemic events leading to discontinuation no upper cutoff day windows are applied.

A listing of patients will be produced and it will display all hypoglycemic events with an onset on or after the start date of double-blind treatment period.

4.2.7.1.6.2 DKA

Separate pages to capture all potential events of DKA, signs and symptoms, and risk factors are contained within the CRF.

DKA events with an onset from Day 1 of the double-blind treatment period up to and including 4 days (30 days for SAE) after the last dose date in the double-blind treatment period will be considered as occurring during the double-blind treatment period. DKA events will be adjudicated, and the proportion of patients with DKA events overall as well as by adjudicated result will be tabulated by treatment group in the double-blind treatment period.

A listing will display all adjudicated DKA events as well as the corresponding signs and symptoms and risk factors with an onset on or after the start date of double-blind treatment period.

4.2.7.2 Clinical Laboratory Tests 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 test) after the last double-blind dosing date will be considered as obtained during the double-blind treatment period. Laboratory data obtained from the day after the last study medication +4 days (30 days for liver function laboratory test) 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 patients with elevated liver test (see Appendix C for definition) will be provided for the double-blind treatment period. In addition, a summary of proportion of patients with elevated liver test and/or reported AE of hepatic disorder will also be provided for the double-blind treatment period.

All scheduled laboratory evaluations are performed by central laboratories. All laboratory evaluations performed by central laboratories will be included in summary tables.

Laboratory parameters will be presented in international system units, except for those listed in Table 16, which will be presented in conventional units (C) and international system units (SI).

Table 16 SI and C units

Test name	SI unit	C unit
FPG	mmol/L	mg/dL
CCI [redacted]		
Total Bilirubin	umol/L	mg/dL
Serum creatinine	umol/L	mg/dL
Urine creatinine	mmol/L	mg/dL
CCI [redacted]		
Phosphate	mmol/L	mg/dL

CCI [redacted]

4.2.7.2.1 Marked Laboratory Abnormalities

Laboratory abnormalities will be evaluated based on marked abnormality (MA) criteria. Appendix C (Laboratory Abnormality Criteria) lists the pre-defined criteria for MAs. If both the baseline and on-treatment values of a parameter are beyond the same MA limit for that 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, and the on-treatment value is beyond the high MA limit (or vice-versa), then the on-treatment value will be considered a MA. If the baseline value is not beyond either MA limit, and the post-baseline value is beyond either MA limit, then the post-baseline value will be considered MA.

Laboratory MAs occurring during the double-blind treatment period will be summarized by treatment group for primary and sensitivity safety analysis. The directions of changes (high or low) in MAs will be indicated in the tables.

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

4.2.7.2.2 Changes from Baseline Values for Selected Laboratory Parameters over Time

All analyses of laboratory data will use observed data regardless of rescue. Visit windows are provided in Section 4.3.1 in order to link each laboratory test to a scheduled visit. Change from baseline during the double-blind treatment period and the follow-up period for selected laboratory parameters will be summarized by treatment group, presenting n's, means, medians, minimum, maximum, SEs:

Hematology parameters:

- hemoglobin
- hematocrit
- red blood cell (RBC) count
- white blood cell (WBC) count
- platelet count

Serum Chemistry parameters:

- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- alkaline phosphatase
- total bilirubin
- blood urea nitrogen (BUN)
- electrolytes - sodium, potassium, bicarbonate, chloride, magnesium, calcium
- total protein and albumin
- creatinine, serum (Scr)
- Estimated eGFR (mL/min/1.73m^2) using MDRD equation

CCI [redacted]

Urine parameters:

- Creatinine

CCI [redacted]

4.2.7.2.3 Additional Laboratory Data Summaries

Shift Tables for Electrolytes (Sodium, Potassium, Calcium, Phosphate, and Magnesium) Categories

Shift tables of Safety Data Set patients 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 rescue) obtained during the double-blind treatment period.

CCI [redacted]

will be summarized by treatment group using the Week 24 values (the last observation regardless of rescue prior to Week 24 will be used if no Week 24 measurement is available).

4.2.7.3 Electrocardiograms

The 12-lead ECG is performed at Visit 2 only. Listings of ECG interpretations will be generated on request.

4.2.7.4 Vital Signs

Unless otherwise specified, vital signs and other physical data obtained after the start of study medication dosing up to 4 days (inclusive) after the last double-blind dosing date will be considered as obtained during the double-blind treatment period. Vital signs and other physical data obtained from the day after the last study medication +4 days (exclusive) up to the last visit date of the follow-up period will be considered as obtained during the follow-up period.

Visit windows are provided in Section 4.3.1 in order to link each vital sign measurement to a scheduled visit.

The values and changes from baseline for systolic and diastolic blood pressures and heart rate will be summarized by treatment group at each scheduled visit using descriptive statistics (using available data regardless of rescue for patients in Safety Data Set).

Number and percentages of patients with orthostatic hypotension (fall in systolic blood pressure of >20 mmHg or diastolic blood pressure of >10 mmHg (supine to standing)) will be summarized by treatment group at each scheduled visit using available data regardless of rescue in Safety Data Set. All observations regardless of distance to the target in each scheduled visit window will be used for the summary of orthostatic hypotension.

Changes from baseline in weight, BMI, CCI [redacted] will be summarized presenting n's, means, medians, minimums, maximums, and SEs, at each scheduled visit during the double-blind treatment period and the follow-up period.

4.2.7.5 Pregnancy Test Results

A by-patient listing of pregnancy test results will be provided using Safety Data Set.

4.3 Conventions

4.3.1 Visit and Period Windows

Patients do not always adhere strictly to the visit timing in the protocol. Therefore the designation of visits during the double-blind treatment period and follow-up period will be based on the day of evaluation relative to the reference start date rather than the nominal visit recorded in the CRF.

To assign a measurement to a Week t during a study period, the first step consists of selecting all measurements falling within this study period as defined below. To further determine the Week t measurement, mutually exclusive relative day windows are used.

The day windows are defined to provide derived visits that correspond to the post-baseline time points specified in the protocol. As already stated, some restrictions may exist on some laboratory assessments to be included in efficacy analyses. These restrictions will be reflected in the day ranges. For example, since no HbA1c is to be collected at Week 1, the windows for HbA1c will only start at Week 4. No Week 1 windowing will be defined.

For each visit, a window will be defined such that the lower and upper bounds of each window is generally the midpoint between 2 consecutive study visits. The visit windows and applicable study day ranges are presented below in Table 17.

Table 17 Visit Windows

Visit	Target Day	Adjusted windows for analyses		
		A1C **FPG** **Safety Laboratory**	**Vital Signs** **Weight** **BMI** CCI [redacted]	CCI [redacted]
Baseline	1	≤1	≤1	≤1
Week 1	8		2-18*	
Week 4	29	2-57*	19-57*	
Week 12	85	58-127*	58-127*	
Week 24	169	128-Last day of DB period	128- Last day of DB period	2- Last day of DB period
Follow-up Week 27	190	Day 1 of FU period-- Last day of FU period	Day 1 of FU period-- Last day of FU period	Day 1 of FU period-- Last day of FU period

*: before the last day of DB period.

For some efficacy parameters, the use of double-blind treatment observations is specified in Section 4.3.2. This section defines the last day after treatment for which these observations are included in the visit window.

For assignment of data to time points using the visit windows, study day will be defined as follows:

(Date of assessment - Date of first dosing) + 1.

In case of multiple observations within a single visit window, the following rules apply:

- If there are two or more observations within the same visit window, the observation closest to the target day will be used in the analysis
- If two observations are equidistant from the target day and the ties are on different sides of the target day, the observation with the earlier assessment date will be used in the analysis
- If two observations are equidistant from the target day and the ties located on the same sides of the target day (i.e. more than one observation for the same day but different time), the observation with the earlier (if the assessment day is equal or

larger than the target day) or later (if the assessment day is smaller than the target day) assessment time will be used in the analysis

- If two or more observations are collected on the same day, all non-missing but with no collection time associated with at least one of them, the average of the observations will be used in the analysis.

- If two or more observations are collected on the same day and time, and they are same closest to the target day, the average of the observations will be used in the analysis.

If a visit window does not contain any observation, then the data will be missing for that visit.

CCI [redacted] visit date, then the average of the available non-missing measurements with that same visit date will be used in summary and analysis.

4.3.2 Post-Dosing Efficacy Observations

While double blind treatment period efficacy observations will be listed regardless of whether the patient was taking blinded study drug. Observations will be included in summarizes of the FAS only if the following rules are satisfied:

- HbA1c, body weight, BMI and CCI [redacted] will be summarized only if measured on or before the 8th day after the last double-blind drug dosing date.

- FPG, CCI [redacted] SBP, eGFR and Insulin initiation will be summarized only if measured on or before the 1st day after the last randomized, double-blind drug dose date.

- Lipids and other exploratory parameters (if available) will be summarized only if measured on or before the 4th day after the last randomized, double-blind drug dose date.

- The efficacy measurements of HbA1c and FPG will be summarized/analysed only if measured on or prior to the first dose of rescue medication.

4.3.3 Assignment of Dates to Adverse Events and Laboratory Assessments

In case of missing dates and/or times, imputation rules will be applied as follows:

For AEs, a missing or incomplete onset date will be imputed according to the following conventions:

1. If the onset date for an AE is missing or incomplete, an imputed date will be derived to slot the event to an appropriate analysis period. This derived date will not be reported in summary tables or listings.

Exception: No dates will be imputed for SAEs. Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

2. If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):

- First active study medication date
- Consent date
- Visit date corresponding to the visit at which the event was reported.
- If a valid non-missing date is not available for any of these dates, the derived onset date will be set to missing.

3. If an onset date is incomplete, the derived onset date will be calculated using the following algorithm:

- Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence):
  - First active study medication date
  - Consent date
  - Visit date corresponding to the visit at which the event was reported
  - If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing.
- Based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.
- If the surrogate date is non-missing then:
  - If the derived date is on or after the surrogate date use the derived date as calculated
  - If the derived date is before the surrogate date and the surrogate date is consistent with the partial data provided for the onset date, use the surrogate date as the derived date
  - If the derived date is before the surrogate date and the surrogate date is not consistent with the partial data provided for the onset date then set the derived onset date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If a year and month is provided, set the derived date to the last day of that month.

- If all three dates used to determine the surrogate date are missing, then based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.

4.3.4 Displays of Vital Signs

At each applicable visit, vital signs systolic and diastolic blood pressures and pulse rate are to be measured three times. Only the means of the individual values, rather than the values themselves, will be summarized.

4.3.5 Calculation of Body Mass Index

The BMI is defined as:

$$\text{BMI} = (\text{weight in kilograms})/(\text{height in meters})^2$$

BMI values will not be rounded to whole integers.

4.3.6 Missing Dates Assessment for Concomitant Medications

Start and stop dates for all concomitant medications are collected on the CRF. However, in case of missing or partial information in these dates, the following rules will be used:

If start date is missing or partial:

- if month is missing, use January (01)
- if day is missing, use the 1st (01)
- if year is missing, use year of the entry visit (consent date for those missing entry visit)
- if entire date is missing, use consent date

If stop date is missing, partial or "continuing:"

- if month is missing, use December (12)
- if day is missing, use the last day of the month under consideration
- if year or the entire date is missing or if "continuing", we leave the date as missing.

Imputed dates will not appear on the tables of non-study medication.

Imputed dates will be reviewed within the study team and agreed by the study team prior to the study being unblinded.

4.3.7 Fasting State

CCI [redacted] fasting plasma glucose, only assessments documented with the patient in fasting state will be summarized and listed. The patient will be determined to be fasting using the response to the question "Was the patient fasting?" in the Central Lab Data Transfer Specification. If the response is not marked, the patient is assumed not fasting.

4.3.8 Counting Rules for Adverse Events

1) Where a patient has the same AE, based on preferred terminology, reported multiple times in a single analysis period, the patient will only be counted once at the preferred terminology level in AE frequency tables.

2) When a patient has the same AE, based on preferred terminology, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- **Relationship to study medication**: Related events will take precedence over unrelated events in determining the event to include in summary tables.
- **Intensity of event:** More intense events will take precedence over less intense events in determining the event to include in summary tables. Missing intensity will be considered the least intense event.
- **Onset date and time:** Earlier onset date-time events will take precedence over later onset date-time events in determining the event to include in summary.

3) When reporting AEs by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Intensity of event
- Onset date and time

4.3.9 Strip Sign for Selected Laboratory Data

For selected laboratory test values that have been received with an operator sign as a part of the result (>, ≥, <, or ≤), 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 will remain as such on the CRF (or in the electronic record) and in the database.

The applicable laboratory tests and applicable operator signs are listed in Appendix D. Additional laboratory parameters can be approved to be added in strip sign plan later along the progress of this study. Unless otherwise specified, for laboratory parameters not included in any statistical analyses, operator signs will not be stripped and the value will counted as missing.

4.3.10 Missing Insulin Dose

For patients who took insulin before or during the study, the mean total insulin dose should be collected in the CRF which includes the dosing values with start and end dosing date. If there are missing dosing values or date gaps during the insulin treatment period, linear interpolation will be used to fill in the missing doses or missing days. The interpolated values will be used to determine if the increase of ≥10% increase in insulin occurred for those patients.

5. INTERIM ANALYSES

No interim analysis was planned.

6. CHANGES OF ANALYSIS FROM PROTOCOL

No changes of analysis from the latest version of protocol.

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8. APPENDICES

Appendix A Criteria for Assessing Important Protocol Deviations

Number	Important Protocol Deviations (IPD) Criteria
CCI	[redacted]

Number	Important Protocol Deviations (IPD) Criteria
CCI	[redacted]

Appendix B Geographic Regions

Geographic Region	Countries
North America	Canada United States
Europe	Italy Spain Sweden Bulgaria Poland Czech

Appendix C Marked laboratory abnormalities

Clinical laboratory variables will be summarized and listed using the units listed here. The criteria for marked abnormality for each variable are listed in the following table. Note that a post-baseline lab value will be considered a MA only if it satisfies the specified criteria and is more **extreme (farther from the limit) than is the baseline value.**

Some parameters units are presented in SI and C, indicating that analyses will be done with both units.

Clinical Laboratory variables	Units	Marked Abnormality Criteria	
		Low	High
Hematology			
HCT males/females	RATIO	<0.2 RATIO	>0.55 RATIO
HCT males/females	RATIO		>0.6 RATIO
Hemoglobin males/females	g/L	<60 g/L	>180 g/L
Hemoglobin males/females	g/L		>200 g/L
Blood Chemistry			
Albumin	g/L	⩽20 g/L	>60 g/L
Total protein	g/L		>100 g/L
ALP	U/L		>3X ULN
ALT	U/L		>3X ULN
AST	U/L		>3X ULN
ALT	U/L		>5X ULN
AST	U/L		>5X ULN
ALT	U/L		>10X ULN
AST	U/L		>10X ULN
ALT	U/L		>20X ULN
AST	U/L		>20X ULN
Total Bilirubin	umol/L (SI) mg/dL (C)		>2X ULN if PreRx ⩽ULN; >3X ULN if PreRx >ULN
Glucose, Plasma Unspecified	mmol/ L (SI) mg/dL (C)	<2.997 mmol/L (SI) <54 mg/dL (C)	>19.425 mmol/L (SI) >350 mg/dL (C)
Na (Sodium)	mmol/L	<130 mmol/L	>150 mmol/L

Clinical Laboratory variables	Units	Marked Abnormality Criteria	
		Low	**High**
Na (Sodium)	mmol/L	<120 mmol/L	
K (Potassium)	mmol/L	⩽2.5 mmol/L	⩾6.0 mmol/L
HCO3 (Bicarbonate)	mmol/L	⩽13 mmol/L	
BUN UREA	mmol/L		>21.42 mmol/L
Creatinine	umol/L (SI) mg/dL (C)		⩾1.5X PreRx CREAT
Creatinine	umol/L (SI) mg/dL (C)		⩾221 umol/L (SI) ⩾2.5 mg/dL (C)
CK (Creatine Kinase)	U/L		>5X ULN
CK (Creatine Kinase)	U/L		>10X ULN
Calcium	mmol/L	<1.87125mmol/L	⩾0.2495 mmol/L from ULN and ⩾ 0.12475 mmol/L from PreRx CA
Magnesium	mmol/L	<0.5mmol/L	>2mmol/L
PO4 (Phosphate)	mmol/L (SI) mg/dL (C)	Age 17-65: ⩽0.58122 mmol/L (C) ⩽1.8 mg/dL (SI) Age ⩾66: ≤ 0.67809 mmol/L (C) ≤ 2.1 mg/dL (SI)	Age 17-65: ⩾ 1.80824 mmol/L (C) ⩾ 5.6 mg/dL (SI) Age ⩾66: ⩾ 1.64679 mmol/L (C) ⩾ 5.1 mg/dL (SI)
Urine			
CCI			

Appendix D Laboratory Tests in Strip Sign Plan *

Lab tests in strip sign plan	Test Code	Operator Sign & Limit of Quantification
CCI		