AstraZeneca

A 52-Week, Multi-Centre, Randomised, Parallel-Group, Double-Blind, Active-Controlled, Phase IV Study to Evaluate the Safety and Efficacy of Dapagliflozin or Dapagliflozin plus Saxagliptin compared with Sulphonylurea all given as Add-on Therapy to Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycaemic Control on Metformin Monotherapy

A 52-Week, Multi-Centre, Randomised, Parallel-Group, Double-Blind, Active-Controlled, Phase IV Study to Evaluate the Safety and Efficacy of Dapagliflozin or Dapagliflozin plus Saxagliptin compared with Sulphonylurea all given as Add-on Therapy to Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycaemic Control on Metformin Monotherapy

Redacted

A 52-Week, Multi-Centre, Randomised, Parallel-Group, Double-Blind, Active-Controlled, Phase IV Study to Evaluate the Safety and Efficacy of Dapagliflozin or Dapagliflozin plus Saxagliptin compared with Sulphonylurea all given as Add-on Therapy to Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycaemic Control on Metformin Monotherapy

Redacted

TABLE OF CONTENTS   PAGE

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	American Diabetes Association
AE	adverse event
AEOSI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AZDD	AstraZeneca Drug Dictionary
β-hCG	beta human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
CI	confidence interval
CrCl	creatinine clearance
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CSRAF	clinical supplies return authorisation form
CV	cardiovascular
DDFM	denominator degrees of freedom
DILI	drug-induced liver injury
E-code	enrolment code
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
FPG	fasting plasma glucose
GAD	glutamate decarboxylase
GLP-1	Glucagon-like peptide-1
H_A	alternative hypothesis
Hb	haemoglobin
HbA1c	haemoglobin a1c
HDL	high-density lipoprotein

Abbreviation or special term	Explanation
HDPE	high-density polyethylene
HFS-II	Hypoglycaemia Fear Survey
H_0	null hypothesis
HR	heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	investigational product
IR	immediate-release
IRB	Institutional Review Board
IWQOL	Impact of Weight on Quality of Life
IWRS	Interactive Web Response System
LDL	low density lipoprotein
LOCF	Last-Observation-Carried-Forward
MAR	missing at random
MCS	Mental Health Component Summary
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	Mixed Model Repeated Measures
MODY	maturity onset diabetes of the young
MTD	maximum tolerated dose
OAD	oral antidiabetic
PCS	Physical Health Component Summary
PP	Per protocol
PPG	postprandial glucose
PRO	patient reported outcome
PT	Preferred Term
QD	once daily
RPD	Relevant Protocol Deviation
SAE	serious adverse event
SAP	Statistical analysis plan
SBP	Systolic Blood Pressure

Abbreviation or special term	Explanation
SCr	serum creatinine
SD	standard deviation
SF-36	Short Form 36-item Health Survey
SGLT2	sodium glucose cotransporter 2
SOC	system organ class
SU	sulfonylurea
T2DM	Type 2 diabetes mellitus
T4	thyroxine
TB	total bilirubin
TZD	thiazolidinedione
UACR	Urinary Albumin to Creatinine Ratio
ULN	upper limit of normal
US	United States
UTI	Urinary Tract Infection
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential
N	Total sample size
NA	Not applicable
Variable	A characteristic or a property of a patient that may vary e.g. from time to time or between patients

AMENDMENT HISTORY

Date	Brief description of change
30Jan2017	SAP updated in alignment with Protocol Amendment 3 (issued 01Nov2016) and Protocol Amendment 4 (issued 12Jan2017).
20Mar2017	Further clarification of RPDs, addition of a secondary efficacy variable and addition of summary tables over time for Glimepiride dose levels and hypoglycaemic events.

1.   STUDY DETAILS

The present Statistical Analysis Plan (SAP) outlines the variables and methods used for evaluating the safety and efficacy of dapagliflozin or dapagliflozin plus saxagliptin compared with sulphonylurea (glimepiride) as add-on therapies to metformin in adults with type 2 diabetes who have inadequate glycaemic control on maximum tolerated dose (MTD) of ≥1500 mg of metformin monotherapy.

1.1   Study objectives

1.1.1   Primary objective

To compare the absolute change from baseline in HbA1c at week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin.

1.1.2   Secondary objectives

- To compare the proportion of patients reporting confirmed hypoglycaemia episodes during the 52-week treatment period between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin
- To compare the change from baseline in total body weight at week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin
- To compare the change from baseline in FPG at week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin
- To compare the time to rescue treatment among the treatment groups during the 52 week treatment period between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin

1.1.3   Other secondary objectives

To compare the effects of dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin on the:

- Proportion of patients achieving HbA1c of <7% (and <7.5%) without confirmed hypoglycaemia at week 52
- Proportion of patients achieving HbA1c of <7% (and <7.5%) at week 52
- Proportion of patients achieving individually agreed HbA1c targets at week 52
- Proportion of patients achieving an HbA1c decrease of ≥1% with no weight gain at week 52
- Time spent below HbA1C target (<7%) (and <7.5%) during the 52-week double-blind treatment period
- Change in body mass index (BMI) from baseline to week 52

- Proportion of patients achieving weight reduction of ≥5% from baseline to week 52
- Proportion of patients with weight gain ≥5% from baseline to week 52
- Proportion of patients reporting at least 1 episode of hypoglycaemia (confirmed hypoglycaemia = symptomatic + blood glucose ≤50 mg/dL, major, other hypoglycaemia) during the 52 week double-blind treatment period
- Change in waist circumference from baseline to week 52
- Change in systolic BP from baseline to week 52

1.1.4 Safety objectives

To evaluate the safety and tolerability of dapagliflozin and dapagliflozin plus saxagliptin versus glimepiride, all as add-on therapy to metformin, during the 52-week treatment period on the:

- Proportion of patients withdrawing from study treatment due to hypoglycaemia
- AEs/SAEs
- AEs of special interest (AEOSI)
- Clinical laboratory tests
- Electrocardiogram (ECG)
- Vital signs (pulse and blood pressure [BP])
- Hypoglycaemic events
- Physical examinations, including incidence of oedema

1.1.5 Exploratory objectives

To explore the mean change from baseline to week 52 in quality of life patient reported outcomes (PROs) and waist-to-hip ratio at week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin.

1.2 Study design

This is a 52-week, multi-centre, randomised, parallel-group, double blind, double-dummy, active-controlled phase IV trial to study the efficacy and safety of dapagliflozin added to metformin and dapagliflozin plus saxagliptin added to metformin compared with sulphonylurea (SU [glimepiride]) added to metformin in adult patients with Type 2 diabetes mellitus (T2DM) - who have inadequate glycaemic control on maximum tolerated dose (MTD) of ≥1500 mg of metformin monotherapy.

The study's duration will be at least 58 weeks, including a 1 week non-obligatory pre-study screening period; a 2-week enrolment period; a 52-week double blind treatment period and a 3-week safety follow-up period.

Figure 1 and Table 1 show the study's flow chart and the detailed study plan respectively.

Figure 1. Flow chart of patients
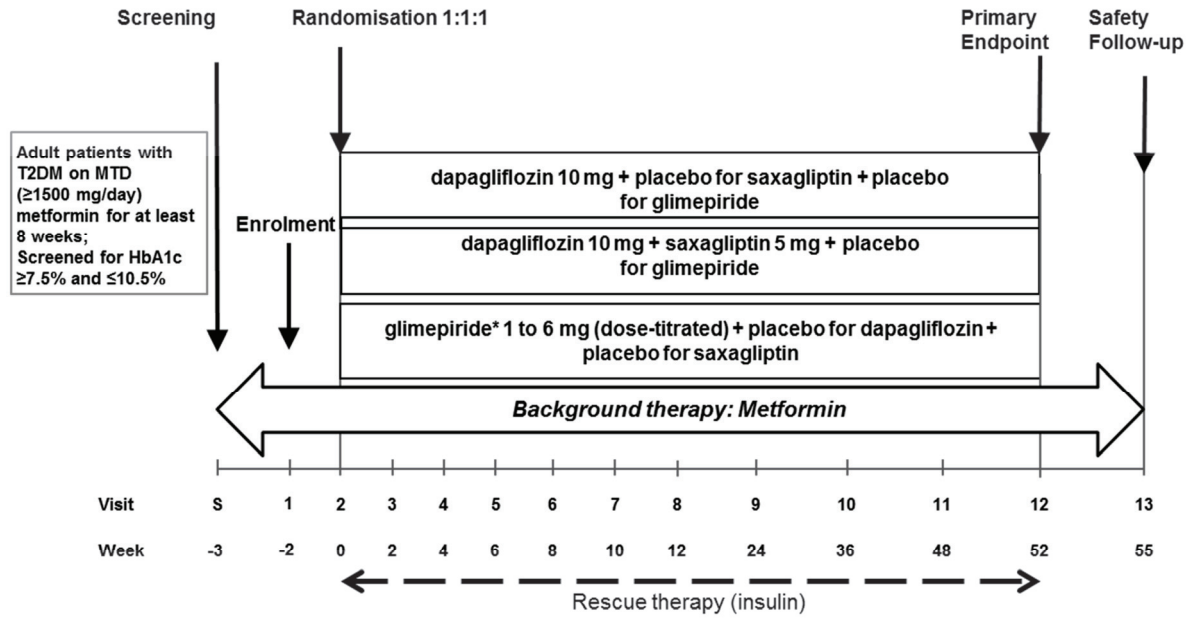
*Note: Glimepiride treatment will begin at 1 mg/day then be titrated (upwards or downwards) in 1 mg increments at subsequent visits, if needed. In the event that a subject develop recurrent hypoglycaemic episodes with the 1 mg dose, down-titration to 0 mg is allowed during the study

Abbreviations: HbA1c haemoglobin A1c, MTD maximum tolerated dose, T2DM Type 2 diabetes mellitus.

Table 1. Study plan

Visit	Screening	Enrolment	R/Baseline	52-week Double-blind Treatment Period									EOT/Rescue[a]	Safety Follow-up
	S^b	1	2^c	3	4	5	6	7	8	9	10	11	12	13
Weeks	-3	-2	0	2	4	6	8	10	12	24	36	48	52	55
Visit window (days)^d	±3	±3	-	±3	±3	±3	±3	±3	±3	±4	±4	±4	±7	±7
Informed consent	X^e													
Assign E-code		X												
Demography and medical history		X												
Inclusion/ exclusion criteria		X	X											
Randomisation			X											
Brief physical examination				X	X	X	X	X	X	X	X	X		X
Complete physical examination		X	X							X			X	
Vital signs (BP, pulse)		X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X	X											
BMI		X	X										X	
Waist and hip circumference			X										X	
12-lead ECG		X	X										X	
Concomitant medications^f	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	Screening	Enrolment	R/Baseline	52-week Double-blind Treatment Period									EOT/Rescue[a]	Safety Follow-up
	S[b]	1	2[c]	3	4	5	6	7	8	9	10	11	12	13
Weeks	-3	-2	0	2	4	6	8	10	12	24	36	48	52	55
Visit window (days)[d]	±3	±3	-	±3	±3	±3	±3	±3	±3	±4	±4	±4	±7	±7
Clinical chemistry[g]		X	X						X	X	X	X	X	X
Haematology		X	X										X	X
HbA1c	X	X	X	X	X	X	X	X	X	X	X	X	X	
Creatinine (to calculate CrCl and eGFR)		X	X	X	X	X	X	X	X	X	X	X	X	X
FPG (local laboratory)			X	X	X	X	X	X	X	X	X	X	X	
FPG (central laboratory)		X	X	X	X	X	X	X	X	X	X	X	X	X
Lipids[h]		X	X										X	X
C-peptide		X												
Hepatitis screening panel[i]		X												
TSH		X												
Urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (urine, WOCBP only)		X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic events		X	X	X	X	X	X	X	X	X	X	X	X	X
Discuss individual targets for glucose control (FPG and HbA1c)			X											
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X

16

Visit	Screening	Enrolment	R/ Baseline	52-week Double-blind Treatment Period										EOT/ Rescue[a]	Safety Follow-up
Visit	S[b]	1	2[c]	3	4	5	6	7	8	9	10	11	12	13	
Weeks	-3	-2	0	2	4	6	8	10	12	24	36	48	52	55	
Visit window (days)[d]	±3	±3	-	±3	±3	±3	±3	±3	±3	±4	±4	±4	±7	±7	
Diet and lifestyle advice		X	X	X	X	X	X	X	X	X	X	X	X		
Dispense glucometer and/or supplies; provide instructions		X	X	X	X	X	X	X	X	X	X	X			
Dispense patient diary		X	X	X	X	X	X	X	X	X	X	X			
Dispense study medication			X	X	X	X	X	X	X	X	X	X			
Register actual glimepiride dosage in IWRS				X	X	X	X	X	X	X	X	X	X		
Patient diary review for glucometer values/ hypoglycaemic events			X	X	X	X	X	X	X	X	X	X	X		
Perform SF-36 survey			X							X			X		
Perform Hypoglycaemia Fear Survey-Worry Scale			X							X			X		
Perform IWQOL-Lite			X							X			X		
Collect unused study medication/supplies													X	X	
Dispense rescue medication (if necessary)					X	X	X	X	X	X	X	X	X		

17

Abbreviations: AE adverse event, Base baseline, BP blood pressure, BMI body mass index, CrCl creatinine clearance, E-code enrolment code, ECG electrocardiogram, eGFR estimated glomerular filtration rate, EOT end of treatment, FPG fasting plasma glucose, HbA1c haemoglobin A1c, HDL high-density lipoprotein, IWQOL Impact of Weight on Quality of Life, IWRS Interactive Web Response System, LDL low-density lipoprotein, R randomisation, SAE serious adverse event, SF short form, TSH thyroid stimulating hormone, WOCBP women of child-bearing potential.

[a]Early Termination procedures are to be completed for all patients who terminate the study or are rescued before Visit 12 (Week 52) of the Treatment Period.

[b]An optional Screening visit (Visit S) may occur within 1 week prior to Enrolment (Visit 1) to screen for eligibility based on a non-fasting sample of HbA1c in patients that do not have a recent HbA1c value (within 30 days).

[c]Visit 2 (Randomisation/Baseline) should be performed within 14 days after Enrolment visit, when laboratory results from Visit 1 are available.

[d]Once a patient is randomised at Visit 2, all visits should be scheduled relative to Visit 2.

[e]An abbreviated informed consent form will be signed at Screening visit.

[f]Review of concomitant medications includes over the counter drugs and herbal/nutritional therapies

[g]Specifications of clinical chemistry laboratory parameters are detailed in CSP Section 5.2.1.3. Visits 1 and 8 to 11 have the same parameters; Visits 2, 12, and 13 have the same parameters; and no clinical chemistry is performed at Visits 3 through 7. CrCl and eGFR will be calculated at all visits.

[h]Serum lipid panel will include LDL-cholesterol, HDL-cholesterol, triglycerides, and total cholesterol.

[i]Hepatitis panel includes hepatitis B viral antibody IgM, Hepatitis B surface antigen, and hepatitis C virus antibody.

Visit windows for the analysis of efficacy and safety variables are described in detail in Section 4.11.2.

The study will be run at approximately 250 sites mainly in Germany and European Union (EU). Approximately 930 patients (310 patients per treatment group) are planned for randomisation to ensure that at least 290 patients per treatment group are evaluable in the Full Analysis Set (assuming 5% exclusion rate from Full Analysis Set). Assuming however that approximately 30% of screened patients will fail the entry criteria, a total of (approximately) 1329 patients will be enrolled.

Sites will be allowed to perform a pre-study screening assessment (at Week -3) prior to enrolment visit to screen for HbA1c criteria. All potentially eligible patients will be enrolled, provide informed consent, undergo screening for all applicable inclusion/exclusion criteria, and submit laboratory samples at Enrolment (Visit 1, 2 weeks prior to randomisation). Patients should be treated with a stable, maximum tolerated dose of metformin monotherapy (≥1500 mg/day) for at least 8 weeks prior to Enrolment, and remain on the same type and dose of metformin therapy for the duration of the study as the background therapy for all treatment arms, as indicated in Section 1.2.2.

1.2.1 Inclusion and exclusion criteria

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances should there be exceptions to this rule. Patients must be receiving metformin (≥1500 mg/day) for treatment of T2DM in accordance with the product label for their country. Eligible patients will be enrolled and examined for all inclusion and exclusion criteria. A full list of the inclusion/exclusion criteria is presented in Appendix II.

1.2.2 Treatment assignment

Patients who meet the study's inclusion and exclusion criteria will be randomised with a 1:1:1 ratio to the following treatment groups:

- Dapagliflozin 10 mg + placebo for saxagliptin + placebo for glimepiride;
- Dapagliflozin 10 mg + saxagliptin 5 mg + placebo for glimepiride;
- Glimepiride (starting at 1 mg dose and titrated up to 6 mg, if needed) + placebo for dapagliflozin + placebo for saxagliptin

The randomisation codes will be computer generated by AstraZeneca R&D using the AZ Global Randomisation system (GRand) and loaded into the IVRS/IWRS database.

Randomisation will be done via IVRS/IWRS at Visit 2. The IVRS/IWRS will allocate randomisation codes centrally as patients become eligible for randomisation.

If a randomisation number is allocated incorrectly, no attempt should be made to remedy the error once study material has been dispensed; the patient will continue with the allocated

number and study material. AstraZeneca or representative should be notified as soon as the error is discovered and subsequent patients will continue using the first unallocated randomisation number in the original numbering sequence.

1.2.3   Blinding and unblinding

A double-blind, double dummy technique is used for blinding. Patients, investigator, study site personnel and sponsor personnel involved with data review and analysis will be blinded throughout the study until database lock. The tablets/capsules of both the active control and the placebo will be identical in size, colour, smell and taste while the bottles with the IPs will be labelled with unique identification numbers allocated from the IWRS.

The database will be locked after all patients have completed the study (or have prematurely discontinued) and all outstanding data queries are resolved. The locked database will be unblinded for reporting purposes. In order to protect the integrity of the study, the patients and investigators will not have access to the individual treatment assignments until the study has been completed.

In addition, no member of the study team (either at AstraZeneca, study sites or any clinical research organisation (CRO)) handling data will have access to the randomisation scheme during the conduct of the study – except AstraZeneca personnel generating the randomisation scheme as well as AstraZeneca's Supply Chain Study Management (SCSM), AstraZeneca Global Pharmacovigilance (GPV), and the CRO providing the IWRS and carrying out the packaging and labelling of IPs.

Unless otherwise specified, to maintain the integrity of the study, HbA1c values and urinary glucose values will be masked on laboratory reports to investigators during at least the double-blind treatment period.

The treatment code - indicating the treatment randomisation for each randomised patient - should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

1.2.4   Double-blind treatment period

The double-blind treatment period consists of the following visits:

1.2.4.1   Randomisation and baseline visit (visit 2, week 0):

During this visit the inclusion/exclusion criteria will be verified and a number of assessments/measurements will be carried out (or calculated) including:

- A complete physical examination
- Vital signs (sitting systolic and diastolic BP and pulse)
- Body weight
- Body Mass Index (BMI)
- Waist and hip circumference
- 12-lead ECG
- Review of concomitant medications (including over the counter and herbal/nutritional supplements)
- Blood samples (including clinical chemistry; haematology; HbA1c; serum creatinine (calculated creatinine clearance [Cockcroft Gault formula] and eGFR); FPG (by local and central laboratories); lipids (low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol, triglycerides, total cholesterol)
- Urinalysis
- Urinary pregnancy test (βhCG) for female patients (WOCBP only)
- AEs and SAEs
- Hypoglycaemic events
- Glucose control (based on FPG and HbA1c)

Diet and life-style advice will be provided and patients will be randomly assigned to 1 of 3 treatment groups as described in Section 1.2.2. In addition, the following surveys will be completed, prior to any assessment at this visit:

- SF-36 questionnaire
- Hypoglycaemia Fear Survey (Worry Scale)
- IWQOL-Lite survey

These surveys are described in detail in Section 3.6.

1.2.4.2   Treatment period visits (visits 3 to 11; weeks 2, 4, 6, 8, 10, 12, 24, 36, and 48):

Prior to these visits, patients are required to have fasted overnight (8 to 12 hours), refrain from alcohol intake, intense exercise (24 hours prior to each visit) and tobacco/nicotine use (within 12 hours prior to each visit). Also patients should bring their metformin and study medication and self-administer the latter as directed by study-site personnel.

During these visits, the study medication and when necessary the rescue medication will be dispensed (Table 2) and assessments of all of the previously listed (baseline) parameters will be performed.

Table 2. Schedule of study medication dispensation

	Enrolment	Blinded Study Medication during Randomised Treatment Period										
Visit #	1	2	3	4	5	6	7	8	9	10	11	12
Study Week	W-2	W0	W2	W4	W6	W8	W10	W12	W24	W36	W48	W52
Dapagliflozin or placebo (tablets)	-	X	-	-	-	-	-	X	X	X	X	-
Saxagliptin or placebo (tablets)	-	X	-	-	-	-	-	X	X	X	X	-
Glimepiride or placebo (capsules)[a]	-	X	X	X	X	X	X	X	X	X	X	-

Note: A dash denotes no dispensation of the drug and X denotes that drug will be dispensed at the specified visit.

[a] Glimepiride will be dispensed in 2 bottles; see Table 5

Abbreviations: W week.

Every day during the treatment period, patients will take 4 tablet/capsules: 1 from the dapagliflozin bottle, 1 from the saxagliptin/placebo bottle, and 1 from each of the glimepiride/placebo bottles (Bottle A and Bottle B; see Table 3).

Dose titration

During the treatment period, the blinded glimepiride/placebo dose will be slowly titrated in a stepwise fashion (Table 3) depending on glycaemic control at every visit. It should be titrated to achieve the individual target FPG of the patient (a target of approximately 110 mg/dL [6.1 mmol/L] is recommended). Up titration should not be done in cases of a recent hypoglycaemia episode while down-titration can be done to mitigate recurrent hypoglycaemic events or at any time during the study. If necessary, glimepiride/placebo will be allowed to be down-titrated to 0 mg (i.e., 2 placebo capsules). The treatment can thereafter be up-titrated again during the treatment period.

Down-titration of other blinded study drug and/or background antihyperglycaemic agent will not be allowed at any time during the study.

The other two treatment groups will be given placebo bottles to maintain the study blind.

Table 3. Titrated dose levels and contents of blinded glimepiride or placebo kit

Dose levels	Total Dosage	Bottle A	Bottle B
0	0 mg	Placebo	Placebo
1	1 mg	1 mg	Placebo
2	2 mg	2 mg	Placebo
3	3 mg	1 mg	2 mg
4	4 mg	2 mg	2 mg
5	5 mg	1 mg	4 mg
6	6 mg	2 mg	4 mg
7	Placebo	Placebo	Placebo

Rescue therapy

During the treatment period, patients may be eligible for treatment with open-label rescue medication (insulin) in addition to their blinded treatment regimen to treat ongoing hyperglycaemia. For patients who have not reached their MTD of glimepiride/placebo, up-titration of glimepiride/placebo should be attempted first before rescue is initiated.

Investigators may increase glimepiride/placebo dose or should initiate rescue insulin treatment based on progressively stricter glycaemic criteria according to Table 4:

Table 4. Criteria for rescue therapy during the randomised treatment period

Visit Period	Central Laboratory glycaemic parameters
Week 0 to 12 (after Visit 2 and including Visit 8)	FPG >240 mg/dL (13.3 mmol/L)
Week 12 to 24 (after Visit 8 and including day of Visit 9)	FPG >200 mg/dL (11.1 mmol/L)
Week 24 to 52 (after Visit 9 and including Visit 12)	HbA1c >8.0%

Abbreviations: FPG fasting plasma glucose; HbA1c haemoglobin A1c.

Rescued patients will be given open-label insulin in accordance with the approved product label in the applicable country at the discretion of the Investigator, in addition to their double-blind study medication. Rescued patients will then continue in the double-blind treatment period according to their original visit schedule.

1.2.4.3 End of treatment period visit/early termination visit/ rescue visit (visit 12; week 52):

During this visit, all the previously listed (baseline and at each treatment period visit) parameters will be re-assessed (see Table 1).

1.2.5 Adjudication committees

Two independent adjudication committees, blinded to study treatment, will oversee the study: a) the hepatic adjudication committee and b) the cardiovascular adjudication committee.

The former will determine the probability that drug-induced liver injury (DILI) is the cause of liver-related abnormalities including (but not limited) to hepatic events timely related to death (within 30 days before death); AST and/or ALT >3x ULN and TB >2x ULN (within 14 days of the AST and/or ALT elevation; AST and/or ALT >10x ULN.

The latter committee will use pre-specified criteria – composed of independent cardiologists blinded to study treatment - for performing adjudication for hospitalisation for heart failure.

Further details of these adjudication committees can be found in their respective charters.

1.3 Number of patients

To demonstrate non-inferiority of dapagliflozin plus metformin or dapagliflozin plus saxagliptin plus metformin to glimepiride plus metformin for changes from baseline to week 52 in HbA1c within a non-inferiority margin of 0.30% - assuming a standard deviation 1.0%, and at a 1-sided significance level of 0.025 - 290 evaluable patients will be needed in each treatment group to provide approximately 95% power (given a true difference of zero between dapagliflozin or dapagliflozin plus saxagliptin and glimepiride). The non-inferiority margin of 0.3% as well as a common standard deviation of 1.0% were selected based on information from earlier, similarly designed studies. Assuming that 5% of patients do not have a post-baseline assessment, a total of approximately 930 patients (310 patients per treatment arm) need to be randomised. Moreover, if 30% of screened patients fail to meet screening criteria, a total of 1329 patients need to be screened.

A hierarchical testing procedure will be followed to control type 1 error rate of 0.05. Dapagliflozin plus saxagliptin plus metformin will be tested for non-inferiority first. If dapagliflozin plus saxagliptin plus metformin is non-inferior to glimepiride plus metformin then dapagliflozin plus metformin will be tested for non-inferiority.

2. ANALYSIS SETS

2.1 Enrolled patients set

This consists of all patients who signed informed consent.

2.2   Randomised patients set

This consists of all randomised patients. It is also known as the intention to treat (ITT) population. Patients will be analysed according to the treatment they were originally assigned (based on the ITT principle).

2.3   Full Analysis Set

The Full Analysis Set will include all randomised patients who receive at least one dose of study medication and who have a non-missing baseline value and at least one post-baseline efficacy value (i.e., HbA1c, FPG, weight). Patients will be analysed according to the treatment they were originally assigned (based on the ITT principle).

The Full Analysis set will be used for addressing the non-inferiority claim for the primary efficacy objective and also for the analysis of all secondary objectives.

2.4   Per Protocol Analysis Set

The Per Protocol Analysis Set will be a subset of the Full Analysis Set consisting of patients who do not violate the terms of the protocol (patients who do not have relevant protocol deviations (RPDs, see section 2.6.2). All decisions to exclude patients and/or data from the Full Analysis Set to form the Per Protocol Analysis Set will be made prior to un-blinding the study and agreed by the study team.

The Per Protocol Analysis Set will be used to re-analyse the primary efficacy variable (as a sensitivity analysis).

2.5   Safety Analysis Set

The safety analysis set is defined as all randomised patients who received at least one dose of study medication. Patients will be analysed according to the actual treatment received. If, at any point during the treatment period, a patient received treatment which was different from which they were randomised to, they will be included in the treatment arm which they received for the majority of the treatment period.

The Safety Analysis Set will be used to analyse all safety related variables: adverse events; serious adverse events; adverse events of special interest; discontinuation of study medication due to hypoglycaemia; clinical laboratory tests; electrocardiogram (ECG); vital signs; hypoglycaemic events.

2.6   Protocol Deviations

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.

2.6.1 Protocol deviation monitoring

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

- IMPACT monitoring – These are manually entered protocol deviations identified by the CRA during study conduct.
- Programmed protocol deviations – These are deviations generated by execution of programs written using the predefined deviator descriptions in the SAP and protocol.

2.6.2 Protocol deviation reporting

Protocol deviations will be reviewed in a blinded fashion by the study team prior to database lock. All decisions to exclude patients and/or data from the Full Analysis Set (to form the Per-Protocol Analysis Set) will be made prior to the unblinding of the study and agreed by the study team.

Protocol deviations that are determined to affect the primary efficacy results are deemed relevant protocol deviations (RPDs). A full list of RPDs is described in Table 5.

Table 5. List of Relevant Protocol Deviations (RPDs)

Number	RPD criteria	Exclusion level
1	Randomised patients without type 2 diabetes, or with corticosteroid-induced Type 2 diabetes, or with maturity onset diabetes in young (MODY), or with diabetes insipidus.	Complete exclusion
2*	Randomised patients without a central laboratory HbA1c obtained at the Enrolment visit (Visit 1), or with central laboratory HbA1c <7.5% or >10.5% as measured from sample collected either at Enrolment visit (Visit 1) or at an unscheduled visit prior to visit 2	Complete exclusion
3	Randomised patients who meet one of the following criteria: a) received a metformin dose <1500 mg, or >3000 mg during the 8 weeks prior to enrolment (Visit 1), b) not treated with metformin alone at any time during the 8 weeks prior to enrolment (Visit 1), c) metformin dose was changed during the 8 weeks prior to enrolment (Visit 1)	Complete exclusion
4	Randomised patients who were treated with glucocorticoids equivalent to oral prednisolone $\geq$10 mg (betametasone $\geq$ 1.2 mg, dexametasone $\geq$ 1.5 mg, hydrocortisone $\geq$ 40 mg)/day for more than 7 days within 30 days prior to enrolment (topical or inhaled corticosteroids are allowed)	Complete exclusion
5a	Randomised patients who took antihyperglycaemic medication other than protocol required	Partial exclusion (exclusion would start from the day when

	dapagliflozin/saxagliptin or dapagliflozin or glimepiride in addition to IP (i.e. other antihyperglycaemic medications started after discontinuation of IP are not classed as an RPD) Or	other than CSP required antihyperglycaemic medicine was started)
5b	insulin is used longer than permitted by the CSP and violates the following situations where insulin use is allowed: - For up to 14 days in total during the study and up to 7 consecutive days if patient is unable to take oral medications - For up to 14 days in total during the study and up to 7 consecutive days if there is a documented illness or infection that requires additional therapy for maintaining glycaemic control; - For up to 14 days in total during the study and up to 7 consecutive days if patients have to temporarily stop IP or metformin due to recommendations made in the clinical study protocol - For up to 7 days during hospitalisation. When the reason for hospitalisation is the management of the patient's glycaemic control, treatment with insulin is considered a rescue and is allowed for as long as clinically necessary Or	Partial exclusion (exclusion would start from 8th consecutive day of insulin therapy or 15th day of non-consecutive therapy, whichever is first).
5c	Metformin dose was changed for patients who were randomised and still taking the double-blind study medication.	Partial exclusion (exclusion would start from the date when Metformin dose was changed).
6a	Patients who received incorrect investigational product at any time during the study	Partial exclusion (exclusion would start from the date when the incorrect IP was taken)
6b	Randomised patients who are judged to be noncompliant in terms of overall compliance, i.e., who took less than 80% or more than 120% of their prescribed dose of study medication during the double-blind treatment period.	Complete exclusion
7	Randomised patients who receive no double-blind medication for ≥2 consecutive weeks	Partial exclusion (exclusion would start from the 14th consecutive day the medication was not taken in an interruption)
8	Treatment with systemic glucocorticoids equivalent to oral prednisolone ≥10 mg (betamethasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day for ≥5 consecutive days of therapy.	Partial exclusion (exclusion starts from the 5th day of therapy with the oral steroids provided in the doses higher than equivalent to oral prednisolone).
9a*	If TSH is abnormal and free T4 is missing or abnormal at visit 1 or at an unscheduled visit prior to visit 2	Complete exclusion
9b	TSH was not performed at visit 1 or at an unscheduled visit	Complete Exclusion

prior to visit 2

10	Known condition of congenital renal glucosuria	Complete exclusion
11	Previous randomisation to treatment in the present study (as assessed by exclusion criteria 36)	Complete exclusion
12*	Creatinine clearance (CrCl) of <60 mL/min or missing CrCl result, based on central laboratory results from Visit 1 or at an unscheduled visit prior to visit 2.	Complete exclusion
13*	C-peptide laboratory value of <1.0 ng/mL (0.33 nmol/L; 331 pmol/L) or missing C-peptide result, based on central laboratory results from Visit 1 or at unscheduled visit prior to visit 2.	Complete exclusion
14*	FPG >270 mg/dL (>15 mmol/L) or missing FPG result, based on central laboratory results from Visit 1 or at an unscheduled visit prior to visit 2	Complete exclusion

* If a patient has an unacceptable/missing value at Visit 1 but then has an unscheduled visit prior to Visit 2 with an acceptable value, the patient will not be considered an RPD.

Patients having relevant protocol deviations will be summarised and listed (by treatment group and overall).

Protocol deviations attributed to the GCP violations will be reported in the CSR according to the following definitions:

Table 6. List of GCP violations

Number	GCP criteria	Exclusion level
1	Delay in SAE reporting	NA
2.	Delay in pregnancy reporting	NA
3,	Delay in overdose reporting	NA
4.	Incorrect ICF handling, not in accordance to the CSP	Complete exclusion

In the unlikely case that a patient did not provide signed and dated written informed consent, he/she will be excluded from all summaries.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary efficacy variable

The primary efficacy variable is the change in HbA1c from baseline (week 0) to week 52. Its calculation is described in Section 4.5.3.

3.2 Key secondary efficacy variables

The key secondary efficacy variables are:

1. Proportion of patients reporting at least one episode of confirmed hypoglycaemia (symptomatic + blood glucose ≤50 mg/dL [2.8 mmol/L]), see section 4.9.6) during the double-blind treatment period
2. Change in total body weight from baseline to week 52
3. Change in FPG from baseline to week 52
4. Time to rescue (start of insulin or discontinuation due to lack of glycaemic control) during the 52-week double-blind treatment period. Its calculation is described in Section 4.5.6.

3.3   Other secondary efficacy variables

Other secondary efficacy variables are:

- Proportion of patients achieving HbA1c of <7% (and <7.5%) without confirmed hypoglycaemia at week 52
- Proportion of patients achieving HbA1c of <7% (and <7.5%) at Week 52
- Proportion of patients achieving individually agreed HbA1c targets at Week 52
- Proportion of patients achieving an HbA1c decrease of ≥1% with no weight gain at week 52
- Time spent below HbA1C target (<7%) (and <7.5%) during the 52-week double-blind treatment period
- Change in body mass index (BMI) from baseline to week 52
- Proportion of patients achieving weight reduction of ≥5% from baseline to week 52
- Proportion of patients with weight gain ≥5% from baseline to week 52
- Proportion of patients reporting at least 1 episode of any hypoglycaemia (confirmed = symptomatic + blood glucose ≤50 mg/dL, major, other hypoglycaemia) during the 52-week double-blind treatment period
- Change in waist circumference from baseline to week 52
- Change in systolic BP from baseline to week 52
- Proportion of patients reporting at least one episode of hypoglycaemia (symptomatic + blood glucose ≤70 mg/dL [3.9 mmol/L]), see section 4.9.6) during the double-blind treatment period

3.4   Safety variables

The following safety variables (defined in Section 4.9) will be analysed:

- Incidence of adverse events (AEs) (including serious adverse events (SAEs), Hypoglycaemic AEs and AEs of special interest (AEOSI))
- Proportion of patients withdrawing from study treatment due to hypoglycaemia
- Change from baseline in clinical laboratory parameters
- Change from baseline in vital signs (pulse and blood pressure)

3.5 Pharmacokinetics

NA

3.6 Patient reported outcomes (PROs)

All patients will complete the SF-36v2 Health Survey, HFS-II Worry Scale and the IWQOL-Lite survey. The SF-36 addresses 8 health concepts: physical functioning; role - physical; bodily pain; general health; vitality; social functioning; role - emotional; and mental health. SF-36 also includes a single item that provides an indication of perceived change in health. Its score ranges from 0 to 100 with higher scores indicating better health.

The HF-II measures the fear of hypoglycaemia in adults with T2DM. Items in the HFS-II Worry scale describe the concerns that patients may have about their hypoglycaemic episodes (e.g., being alone, episodes occurring during sleep, or having an accident). Each is measured on a 5 point scale (Never to Always).

The IWQOL-Lite is a 31-item self-reported assessment of quality of life in overweight or obese individuals. It scores on 5 dimensions: physical function (11 items); self-esteem (7 items); sexual life (4 items); public distress (5 items); and work (4 items). A global score (sum of scale scores) is also included. Participants are asked to rate items with respect to the past week on this instrument (from never true to always true). Scores on the IWQOL-Lite (domains and global score) range from 0 to 100 with higher scores indicating poorer quality of life.

The following exploratory endpoints related to patient reported outcomes will be summarised:

- Change in the short form 36-item health survey (SF-36) scores from baseline to week 52
- Change in the Hypoglycaemia Fear Survey (HFS-II) Worry scores from baseline to week 52
- Change in the Impact of Weight on Quality of Life (IWQOL)-Lite survey scores from baseline to week 52

3.7 Additional exploratory endpoints

- Change in waist:hip ratio from baseline to week 52

3.8 Health economics

NA

4. ANALYSIS METHODS

4.1 General principles

Continuous variables will be presented with mean; median; 25th and 75th percentiles; standard deviation (SD); minimum; maximum; and (if appropriate) the number of non-missing observations. Categorical data will be displayed via absolute and relative frequencies for each category, including a category labelled as 'missing' when appropriate. The 'missing' category will not contribute to the denominators of relative frequencies.

Demographic and baseline characteristics will be summarised using frequency distributions and descriptive statistics using the Randomised patients set, for each treatment group as well as for all patients combined. Key baseline characteristics that will be summarised include: age; gender; race; ethnicity; country; body weight; BMI; duration of T2DM; baseline FPG; baseline HbA1c and baseline eGFR. Baseline is defined as the last measurement prior to the first dose of double blind study medication or as the last non-missing value of the visit 1 or visit 2 assessment for those subjects without a first dose start date. No statistical tests will be performed to compare treatment groups at baseline.

4.2 Primary analysis

The primary analysis will be carried out for the primary objective using data from the Full Analysis set. It will use values prior to rescue treatment or discontinuation (more than 8 consecutive days off treatment, see section 4.6.2).

4.2.1 Objectives and hypotheses

The combination of metformin and a sulphonylurea (glimepiride) is a standard therapy in the treatment of type 2 diabetes and has been shown to reduce HbA1c.

The primary objective of this study is to demonstrate the non-inferiority of dapagliflozin and dapagliflozin plus saxagliptin as add-on therapies to metformin compared to glimepiride as add-on therapy to metformin for the primary efficacy variable (change in HbA1c from baseline to week 52).

The null hypothesis H_0 (given below) will be tested against the alternative hypothesis H_A ($\alpha = 0.025$, one-sided):

H_0: $\mu_t - \mu_c \geq 0.30\%$,

H_A: $\mu_t - \mu_c < 0.30\%$

where μ_t denotes the mean absolute change in HbA1c from baseline to week 52 in patients treated with dapagliflozin added to metformin and dapagliflozin plus saxagliptin added to metformin (test medication); μ_c denotes the mean absolute change in HbA1c from baseline to week 52 in patients treated with glimepiride added to metformin (active control). The non-inferiority margin is determined to be 0.30% (in absolute terms). A difference of 0.30% or

less, in HbA1c change from baseline to week 52 between the treatment groups, is considered clinically equivalent (from a medical point of view). Non-inferiority will be assessed using the 2-sided 95% Confidence Interval (CI) of the adjusted mean difference between dapagliflozin or dapagliflozin plus saxagliptin and glimepiride. If the upper limit of the 2-sided 95% CI is less than 0.30% then dapagliflozin or dapagliflozin plus saxagliptin will be considered to be non-inferior to glimepiride.

To preserve the Type I error ≤ 0.025 (one-sided), a hierarchical testing procedure will be used as follows:
- First test dapagliflozin plus saxagliptin versus glimepiride
- If non-inferiority is achieved then test dapagliflozin versus glimepiride

4.3 Secondary analysis

Four key secondary endpoints have been identified:

1. Proportion of patients reporting at least 1 episode of confirmed hypoglycaemia (symptomatic + blood glucose ≤50 mg/dL) during the double-blind treatment period
2. Change in total body weight from baseline to week 52
3. Change in FPG from baseline to week 52
4. Time to rescue during the 52 week treatment period

The hypotheses of the above four key secondary endpoints will test for superiority of dapagliflozin and dapagliflozin plus saxagliptin over glimepiride when used as add-on therapy to metformin - where superiority implies smaller proportions of patients experiencing at least one episode of hypoglycaemia, greater reductions in body weight and FPG; and a longer time to rescue treatment.

A superiority test of the dapagliflozin plus saxagliptin added to metformin group versus the glimepiride added to metformin group will also be conducted for the primary efficacy variable of change in HbA1c from baseline to week 52.

4.3.1 Control of Type I error

The experiment-wise type I error will be controlled to a maximum of 5%. A hierarchical closed testing procedure will be employed such that key secondary endpoints will be considered for statistical significance (in terms of superiority) only if non-inferiority of the primary endpoint is concluded and that a key secondary endpoint will be considered for statistical significance only if the test ordered before it is found to be statistically significant. At each step, dapagliflozin plus saxagliptin added to metformin versus glimepiride added to metformin will be tested first followed by the test for dapagliflozin added to metformin versus glimepiride added to metformin except for the superiority tests of the primary endpoint and the endpoint of total body weight. The test of superiority for HbA1c will include only the comparison of dapagliflozin plus saxagliptin added to metformin vs glimepiride added to metformin. For total body weight, dapagliflozin added to metformin versus glimepiride will

be tested first followed by dapagliflozin plus saxagliptin added to metformin versus glimepiride added to metformin.

The following testing order will be followed for the overall type I error control:

1. Change from baseline in HbA1c at Week 52 (test for non-inferiority)

2. Proportion of patients reporting at least 1 episode of confirmed hypoglycaemia at Week 52 (test for superiority)

3. Change in total body weight from baseline to Week 52 (test for superiority)

4. Change from baseline in HbA1c at Week 52 (test for superiority of dapagliflozin plus saxagliptin added to metformin vs glimepiride added to metformin only)

5. Change in FPG from baseline to Week 52 (test for superiority)

6. Time to rescue at Week 52 (test for superiority)

The statistical comparisons will be done using a comparison-wise type I error of 5% (2-sided). For all other secondary variables and exploratory variables, nominal p-values will be reported without multiplicity controlled significance testing.

4.4   Sensitivity analyses

Sensitivity analyses will be carried out for the primary efficacy endpoint (change in HbA1c from baseline (week 0) to week 52) only. These sensitivity analyses will be as follows

- Mixed Model Repeated Measures (MMRM) using the Per-Protocol analysis set,
- ANCOVA using values prior to rescue treatment (LOCF will be used if the week 52 value is not available)
- The MMRM model will be repeated including all values according to the ITT principle (i.e. all values will be included regardless of use of rescue treatment or treatment discontinuation)

Further details of these sensitivity analyses is provided in Section 4.8.4.

4.5   Definitions

4.5.1   Baseline values

For all efficacy variables, the baseline value will be the last non-missing value on or prior to the first dose of the double-blind study drug date or the last non-missing value of the visit 1 or visit 2 assessment for those subjects without a first dose start date.

The baseline value of each safety laboratory test or physical exam endpoint is defined as the last assessment (either numerical or character value) on or prior to the first dose of double-blind study drug date or the last non-missing value of the visit 1 or visit 2 assessment for those subjects without a first dose start date.

4.5.2   Derived data

The **waist:hip ratio** is calculated as: waist circumference (cm) / hip circumference (cm).

To convert HbA1c from mmol/mol to % the following conversion factor will be used:

HbA1c (%) = (0.09148*HbA1c (mmol/mol)) + 2.152

4.5.3   Change from baseline

Change from baseline to any week t in the double-blind treatment period is defined as follows:

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

where a) $C_{week\ t}$ is the change from baseline at week t, b) $M_{week\ t}$ is the measurement at week t, and c) $M_{baseline}$ is the measurement at baseline.

4.5.4   Longitudinal repeated measures analysis

A longitudinal repeated measures analysis using restricted maximum likelihood (REML) will be performed for the primary efficacy endpoint and three of the secondary endpoints (change in weight from baseline to week 52, change in FPG from baseline to week 52 and change in SBP from baseline to week 52). The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, week and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.

This method involves implementing a linear mixed effects model of the form:

$$C_{ijk} = intercept + \beta_1[M_{baseline,ij}] + \tau_i + \alpha_k + (\alpha\,\tau)_{ik} + (\alpha\,M_{baseline})_{ijk} + error_{ijk}$$

where

- C_{ijk} is the change from baseline for patient j in treatment group i at time k.
- β_1 is the slope coefficient for the baseline measurement
- $M_{baseline,ij}$ is the baseline measurement for patient j in treatment group i
- τ_i is the mean effect for treatment group i
- α_k is the mean effect at time k
- $(\alpha\,\tau)_{ik}$ is the interaction term between treatment group i and time k
- $(\alpha\,M_{baseline})_{ijk}$ is baseline measurement-by-week interaction term for patient j in treatment group i at time k
- $error_{ijk}$ is the error term for patient j in treatment group i at time k

The above model incorporates repeated measures (where measurements are taken repeatedly on the same patient i.e., at baseline, week 2, week 4 up to week 52). Hence, the primary model is a mixed model repeated measures (MMRM). The model will be used to derive a least-squares estimate of the mean treatment difference with corresponding 2-sided 95% CI.

An unstructured matrix for the within-subject error variance-covariance will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (DDFM).

In case of non-convergence of the preferred model or memory space issues, the following back-up models will be 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.

4.5.4.1   Adjustment for baseline imbalances

Clinically important imbalances between treatment groups with respect to baseline characteristics will be identified using summaries of baseline data by treatment group. Any imbalances will be assessed from a clinical perspective (without performing statistical testing). If clinically important imbalances are found (e.g., between countries), they may be adjusted for in the analysis by including the corresponding baseline characteristics as additional covariates in the model, e.g., a fixed effect for country may be added to the MMRM model.

4.5.4.2   Assessment of Treatment-by-Baseline interaction

Treatment-by-baseline interaction will be assessed for the analyses of the primary efficacy endpoint. In the repeated measures model, the interaction will be tested by including the additional terms for the treatment-by-baseline interaction (treatment-by-baseline HbA1c and treatment-by-baseline HbA1c-by-week).

The treatment-by-baseline HbA1c-by-week interaction will be assessed using contrasts of the treatment effect by baseline HbA1c at Week 52. The test for interaction will be performed at the 0.10 level of significance. If the interaction is not significant, the original model will be used (see section 4.5.4). Otherwise, the interaction will be assessed as qualitative or quantitative. Assessment of the interaction type will be based on regression lines plotted for each treatment group. The intercepts and slopes for these regression plots will be obtained from the analysis model including the interaction term. The intercepts will be estimated by the

least squares treatment means. The horizontal axis of the plots will range from the minimum baseline value from all subjects included in the analysis to the maximum baseline value.

If the regression lines do not cross, or the crossing is judged not severe (i.e., the crossing occurs near the boundary or beyond the range of baseline values), then the interaction will be considered quantitative and this does not compromise the validity of the treatment comparisons. In this case, the treatment comparisons will be made using the original model without the interaction term.

Otherwise, the interaction will be considered qualitative and treatment comparisons will not be presented as a result of the original model. In this case, the impact of the baseline value on treatment effect will be investigated by summarizing the data in subsets defined by baseline categories.

4.5.4.3 Subgroup Analyses and Assessment of Treatment-by-Subgroup interaction

Treatment effects will be assessed across the following sub-groups: baseline HbA1c (<8%, ≥8% - <9%, ≥9%), age group (<65, ≥65 - <75, ≥75 yrs), gender, female age group (≤50, >50 yrs), race, country, and baseline eGFR (<30, ≥30 - <45, ≥45 - <60, ≥60 - <90, ≥90 mL/min/1.73m^2). The analyses will be based on the primary model (see section 4.5.4). The estimates within each baseline HbA1c subgroup will come from the model with terms for treatment, week, baseline HbA1c category, treatment-by-week, treatment-by-baseline HbA1c category, time-by-baseline HbA1c category and treatment-by-time-by-baseline HbA1c category. Adjusted mean change from baseline and its difference from the control group will be given for each subgroup at week 52. The model to assess the treatment-by-baseline HbA1c interaction will include baseline HbA1c as a continuous variable (as per section 4.5.4.2).

Treatment effects within the remaining subgroups will come from the model including the fixed categorical effects of treatment, week, subgroup, treatment-by-week, treatment-by-subgroup, time-by-subgroup and treatment-by-time-by-subgroup as well as the continuous fixed covariates of baseline HbA1c and baseline HbA1c-by-week interaction. Tests of the treatment by subgroup interaction will be assessed using contrasts of the treatment effect by subgroups at Week 52. The model to assess the treatment-by-age interaction, the treatment-by-female age interaction and the treatment-by-baseline eGFR interaction will include age/baseline eGFR as a continuous variable.

4.5.5 Analysis of covariance (ANCOVA) for change from baseline

Analysis of covariance (ANCOVA) is used for endpoints examining the change from baseline to week *t* (See Section 4.8.2 and Table 11 for details of endpoints). In this model, the change from baseline (at time point *t*) is a function of the treatment group (fixed effect) and the baseline measure (covariate). The following model will be used:

$$D_{t,ij} = intercept + \beta Y_{0,ij} + \tau_i + error_{ij}$$

where, $D_{t,ij} = Y_{t,ij} - Y_{0,ij}$, the week t change from the baseline of subject j in treatment group i; $Y_{0,ij}$ is the baseline measure of subject j in treatment group i; $Y_{t,ij}$ is the week t measure of subject j in treatment group i; τ_i is the mean effect of treatment group i; *intercept,* β and τ_i are unknown parameters to be estimated from the data.

Ordinary least squares (OLS) will be used to estimate the model's parameters along with two-sided 95% Confidence Intervals (CIs).

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

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

Time to rescue is defined as the time (in days) from the first dose date after randomisation to the date at which the patient first meets the following rescue criterion: (which is confirmed),

  i.   FPG > 240 mg/dL (13.3 mmol/L) for the period after Visit 2 to and including Visit 8 (Week 0 to 12) OR
  ii. FPG > 200 mg/dL (11.1 mmol/L) for the period after Visit 8 to and including day of Visit 9 (Week 12 to 24) OR
  iii. HbA1c > 8% for the period after Visit 9 to and including Visit 12 (Week 24 to 52)

Time to rescue will be censored at the earliest of discontinuation of study medication/study, or study completion, or time of insulin start (for those subjects who received rescue treatment without confirmed rescue criteria).

4.5.7 Analysis of proportions

Proportions endpoints will be analysed using logistic regression with the baseline measure as a covariate. The adjusted percentage with 95% CI, Odds Ratio with 95% CI and nominal p-values for the comparison of dapagliflozin or dapagliflozin plus saxagliptin vs glimepiride will be presented. The confidence intervals will be based on the profile likelihood method. When there are less than 5 responders in any treatment group, the unadjusted proportions (and difference), exact 95% confidence interval, and p-values from the Fisher's exact test (when applicable) will be provided.

4.5.8 Time spent below target HbA1c (<7% and <7.5%)

In order to calculate the time spent below HbA1c target (<7% and <7.5%), linear interpolation will be used to create a profile for the HbA1c values over time for each patient. The amount of time spent <7% (or <7.5%) will then be calculated (in days) from this profile. If there is more

than 1 segment where the patient is below target and then rebounds, the individual segment times will be added together.

Missing intermediate HbA1c values will not be imputed, the interpolation will proceed from the last available value to the next available value. If the week 52 value is missing, there will be no extrapolation of data to this timepoint.

Actual visit dates will be used to determine times between all visits. No time below target will be counted beyond 365 days (52 weeks).

Values recorded after rescue (for those who used rescue medication) or values collected more than 8 days after the last dose date (for patients who stayed more than 8 consecutive days off treatment) will be excluded from these calculations.

4.6 Missing data

4.6.1 Handling missing demographic and baseline characteristics data

For demographic and baseline characteristics, each variable will be analysed and/or summarized using the available data i.e. patients with missing data will be excluded from the summaries.

4.6.2 Handling missing efficacy data

Missing data can result from patients discontinuing the study prematurely or by missing intermediate visits or selected assessments while remaining in the study. To eliminate missing data, every effort will be made to obtain the protocol-required data for all scheduled study assessments for all enrolled patients. For efficacy analyses, the MMRM model assumes missing observations are missing at random (MAR). MAR means that the tendency of a data value to be missing depends only on the observed data, and not on the missing data. For example, if an HbA1c value is missing, it assumes this is not related to the missing data but to some of the observed data (response and covariates) (Ref ([1])).

For the change in HbA1c and weight analyses using MMRM, values recorded after rescue treatment for those patients who used rescue medication or values collected more than 8 days after the last dose date for patients who stayed more than 8 consecutive days off treatment are excluded from the analysis. For the change in FPG analysis using MMRM, values recorded after rescue treatment for those patients who used rescue medication or values collected more than 1 day after the last dose date for patients who stayed more than 1 consecutive days off treatment are excluded from the analysis. For the change in SBP analysis using MMRM, values recorded after rescue treatment for those patients who used rescue medication or values collected more than 4 days after the last dose date for patients who stayed more than 4 consecutive days off treatment are excluded from the analysis.

The MMRM model assumes the time course of the endpoint values for patients who discontinue double-blind treatment or are rescued at a specific time point is consistent with the time course for patients ongoing at that time point.

Summaries of missing data by visit for HbA1c will be provided in order to explore this assumption (see Table 16 provided in Appendix IV).

When performing ANCOVA, the Last Observation Carried Forward (LOCF) method will be used for dealing with missing values i.e. if no Week 52 measurement is available, the last available earlier post-baseline measurement will be used except for the efficacy variable time spent below HbA1c target. For patients who started rescue medication prior to Week 52, their last post-baseline measurement taken prior to the date of the first dose of rescue medication will be used.

For the proportions endpoints regarding glycaemic control at week 52, all available data will be used but patients rescued prior to week 52 will be treated as treatment failures (non-responders). Subjects with missing information at week 52 (e.g. HbA1c, weight) will be counted as treatment failures. For the endpoints 'the proportion of patients with at least one episode of confirmed hypoglycaemia' and 'the proportion of patients with at least one episode of hypoglycaemia (symptomatic with blood glucose ≤70mg/dL [3.9mmol/L]), if the blood glucose value is missing for a patient with hypoglycaemia, they will not be counted as having a confirmed hypoglycaemic event.

Section 4.11 provides additional information regarding handling of missing or partial dates, inclusion of values, visit windowing, and values obtained post treatment.

4.7   Analysis methods

4.7.1   Study population

4.7.1.1   Patient disposition

The disposition of patients for the pre-treatment period and the double-blind treatment period will be summarised. This involves all patients enrolled (who signed informed consent) in the pre-treatment period; all patients randomised to the double-blind treatment period (and those not randomised and reason for not randomised); all patients completing (and discontinuing and reasons for discontinuing) the double-blind treatment period.

4.7.1.2   Demographic and baseline characteristics

Demographic and other baseline characteristics, including diabetes-related characteristics and renal function characteristics, will be summarised and listed by treatment group and overall, using the Randomised Patients Set.

Table 7 describes the demographic and baseline characteristics; Table 8 describes the diabetes-related common baseline characteristics and Table 9 describes the common renal function baseline characteristics.

Table 7. Demographic and baseline characteristics

Characteristic	Type	Categories
Gender	Categorical	Male, Female
Age	Continuous and categorical	< 65 yrs; ≥65 - <75 yrs; ≥75 yrs

Female age	Categorical	≤50 yrs; >50 yrs
Race	Categorical	White; Black or African American; Asian; Other
Ethnicity	Categorical	Hispanic/Latino, Not Hispanic/Latino
Body weight	Continuous	
Height	Continuous	
Waist circumference	Continuous	
Body Mass Index	Continuous and categorical	<25kg/m^2; ≥25kg/m^2; ≥27kg/m^2; ≥30kg/m^2
Country	Categorical	Germany; Slovakia; Hungary; Poland; Czech Republic

Table 8. Diabetes-related baseline characteristics

Characteristic	Type	Categories
Duration of type 2 diabetes	Continuous and categorical	< 3 yrs; ≥3 - ≤10 yrs; >10yrs
HbA1c	Continuous and categorical	<8%; ≥8% - <9%; ≥9%
FPG	Continuous	
C-Peptide	Continuous	

Table 9. Baseline renal function and other characteristics

Characteristic	Type	Categories
eGFR (MDRD)	Categorical and continuous	<30 mL/min/1.73 m^2; ≥30 - <45 mL/min/1.73 m^2; ≥45 - <60 mL/min/1.73 m^2; ≥60 - <90 mL/min/1.73 m^2; ≥90 mL/min/1.73 m^2

4.7.1.3   Specific and general disease histories

The number (percent) of patients with diabetes and diabetes-related disease histories will be summarised and listed by treatment group, and overall using the Randomised Patients Set.

The number (percent) of patients with abnormal general medical history findings will be summarised by treatment group and overall by System Organ Class (SOC) and Preferred Term (PT) using the Randomised Patients Set. Medical History will be coded using the MedDRA dictionary (version 19.1 or later).

4.7.2 Extent of exposure

4.7.2.1 Study medication

The extent of exposure to study medication (investigational products) during the double-blind treatment period is defined as the difference between the last and the first dose of study medication of the double-blind treatment period plus 1 day.

The extent of exposure to study medication will be summarised using the Safety Analysis Set. The number and percent of patients with an extent of exposure within pre-specified day ranges will be presented for the double-blind treatment period by treatment group as follows: 1-6; 7-14; 15-28; 29-42; 43-56; 57-70; 71-84; 85-168; 169-252; 253-336; 337-371, $\geq$372 days. The mean, standard deviation (SD), median and range of the number of days of exposure will also be presented.

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

Dose levels of metformin at randomisation (visit 2) will be summarised for each treatment group (Safety Analysis Set). Dose levels of glimepiride at week 52 and over time will be summarised for this treatment group (Safety Analysis Set).

4.7.2.2 Interruption of study medication

Dates for any interruptions of study drug will be captured on the Exposure (EX) CRF page. Dose interruptions will be summarised for each treatment group (Safety Analysis Set). Down titrations to 0mg glimepiride will be included as interruptions (for the purposes of this summary table only).

4.7.2.3 Dose titrations of Glimepiride

The number of patients with a down-titration will be summarised for the glimepiride plus metformin treatment group (Safety Analysis set).

4.7.3 Current and Concomitant medications

Current and concomitant medications will be summarised 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 (version 16.2 or later). A summary will be produced for each of the following:

- all current medication
- all concomitant medication

Current medications are defined as medications with a start and stop date prior to the first day of double-blind treatment, 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 and stopped prior to the first dose of study medication.

Concomitant medications are defined as a medication with either:

- a recorded medication start date falling within the double-blind treatment period (i.e. a medication started during the double-blind phase), 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 (i.e. a medication started prior to double-blind medication and continued in the double-blind phase).

If missing or partial dates of medication start/stop dates occur, the medication will be assumed to be taken during the double-blind treatment period unless there is convincing evidence to the contrary, i.e. it will be included in the summary table of concomitant medications.

4.7.3.1 Other Treatments

A list of the prohibited medications during the study (and their corresponding time frames) is presented in Table **10**.

Table 10. **List of prohibited medications**

Restricted Medication/Class of drug:	Usage
Sulfonylureas, pioglitazone, rosiglitazone, GLP-1 receptor agonists, any DPP-4 and SGLT2 inhibitors other than IP.	Prohibited during the study.
Insulin therapy (with the exception of insulin therapy during a hospitalisation or use in gestational diabetes).	Use of insulin during the study is only acceptable if given as a rescue treatment as allowed per the protocol (CSP Section 7.8.2) for any duration as clinically necessary, or for a temporary use in the following situations: - For up to 14 days in total and up to 7 consecutive days if patient is unable to take oral medications - For up to 14 days in total and up to 7 consecutive days if there is a documented illness or infection that requires additional therapy to maintain glycaemic control - For up to 14 days in total and up to 7 cconsecutive days if patients have to temporarily stop study medication or metformin due to recommendations made in this protocol - For up to 7 days during hospitalization. When the reason for hospitalisation is the management of the patient's glycaemic control, treatment with insulin is considered a rescue and is allowed for as long as clinically necessary

Restricted Medication/Class of drug:	Usage
Other investigational drugs or participation in any interventional clinical study	Prohibited during the study.
Treatment with systemic glucocorticoids equivalent to oral prednisolone ≥10 mg (betamethasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day	Newly initiation of treatment with any systemic corticosteroid therapy that will involve ≥5 days of therapy (inhaled and topical are allowed). The Medical Monitor should be consulted prior to beginning therapy with corticosteroids for patients who require systemic corticosteroid treatment.
Prescription or over-the-counter weight loss medications	Prohibited during the study.

Other treatments include:

- Metformin

Patients will remain on their pre-study stable, maximum tolerated metformin doses ≥1500 mg/day, during the 52-week double-blind treatment period of the study. Metformin should be administered and stored according to product and country-specific labelling.

Metformin will not be provided in pre-packaged kits by the Sponsor as it is the usual care prior to study participation.

- Rescue therapy

Patients may be eligible for rescue therapy with open-label rescue medication (Insulin) for treating ongoing hyperglycaemia. Patients should continue receiving blinded study medication while receiving rescue therapy. If rescue therapy fails, further therapy will be given at the discretion of the Investigator.

Rescue therapy will be prescribed by the investigator (and not provided by the Sponsor).

- Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the CRF.

4.7.4   Treatment compliance

Percent treatment compliance will be calculated during the double-blind treatment period for each treatment group. For each patient, percent compliance is defined as the number of tablets taken divided by the number of tablets that should have been taken, multiplied by 100.

The number of tablets that should have been taken will be calculated as the double-blind treatment stop date – double-blind treatment start date + 1, multiplied by 4 (since each patient should take 1 tablet per day from each of the 4 bottles).

The number of tablets taken will be calculated as the total number of tablets dispensed minus the total number of tablets returned (i.e. the totals for all 4 bottles).

A patient is considered compliant if percent compliance is $\geq 80\%$ and $\leq 120\%$. The number and percent of patients considered compliant will be summarised for each treatment group using the Safety Analysis Set.

4.8   Efficacy analyses

The following table provides a summary of how each efficacy variable will be analysed:

Table 11   Statistical analyses to be conducted and sensitivity analyses

Efficacy Variable	Analyses
Primary:	
Change in HbA1c from baseline to week 52	**Primary analysis:** MMRM (Full Analysis Set)
	Sensitivity analyses: MMRM (Per Protocol Analysis Set) ANCOVA using values prior to rescue treatment (LOCF used if the week 52 value is not available) MMRM primary model repeated including all values regardless of whether patient used rescue treatment or discontinued treatment
	Subgroup analyses: MMRM with covariates for each of the following: age group, gender, race, country, baseline HbA1c and baseline eGFR
Key Secondary:	
Proportion with at least one episode of confirmed hypoglycaemia	Logistic regression
Change in body weight from baseline to week 52	MMRM
Change in FPG from baseline to week 52	MMRM
Time to rescue	Cox PH model
Other Secondary:	
Proportion achieving HbA1c <7% (and <7.5%) without confirmed hypoglycaemia at week 52	Logistic regression

Proportion achieving HbA1c <7% (and <7.5%) at week 52	Logistic regression
Proportion achieving individually agreed HbA1c targets at week 52	Logistic regression
Proportion with an HbA1c decrease of ≥1% with no weight gain at week 52	Pearson's Chi-square test
Time spent below HbA1c target (<7% and <7.5%)	ANCOVA
Change in BMI from baseline to week 52	ANCOVA (LOCF)
Proportion with a weight reduction ≥5% or a weight gain ≥5% at week 52	Logistic regression
Proportion with at least 1 episode of any hypoglycaemia	Logistic regression
Change in waist circumference from baseline to week 52	ANCOVA (LOCF)
Change in systolic BP from baseline to week 52	MMRM
Proportion with at least one episode of hypoglycaemia (symptomatic with blood glucose ≤70 mg/dL [3.9mmol/L])	Logistic regression

Note: Each analysis is based on the Full Analysis Set unless otherwise stated.

4.8.1 Primary Efficacy Analysis

The primary efficacy variable is the change in HbA1c from baseline to week 52 in the double-blind treatment period. The primary efficacy analysis will be based on the Full Analysis Set including values prior to rescue treatment or discontinuation. Values recorded after rescue treatment for those patients who used rescue medication or values collected more than 8 days after last dose date for patients who stayed more than 8 consecutive days off treatment are excluded from the analysis.

The primary efficacy variable will be analysed using the MMRM model (Section 4.5.4) with fixed effects for treatment group and covariates (baseline HbA1c; week (week 2 to week 52), and interactions baseline HbA1c-by-week and treatment group-by-week). Point estimates and 95% CIs will be calculated for the adjusted mean changes from baseline within each treatment group as well as for each comparison versus control in adjusted mean changes. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (DDFM) while an unstructured variance will be used to model the within-patient errors.

The primary assessments of efficacy will be a comparison of each of the 2 test groups: the dapagliflozin plus saxagliptin added to metformin versus the control group (glimepiride added to metformin) - and the dapagliflozin added to metformin versus the control group - using a 2-sided 95% CI. In particular, if the observed upper limit from a 2-sided 95% CI for the

difference in adjusted means is less than 0.30%, then the test group will be considered to be non-inferior to the control group.

Multiplicity will be controlled using a sequential testing scheme: the dapagliflozin plus saxagliptin added to metformin group will be tested versus the glimepiride group first, followed by the dapagliflozin plus metformin group versus the glimepiride group. If the first comparison is non-inferior the second comparison will be tested. Otherwise, significance testing will stop at the first comparison and the second comparison will be reported descriptively. See Section 4.2.1 for details. A superiority test of the dapagliflozin plus saxagliptin added to metformin group versus the glimepiride added to metformin group will also be conducted using the same modelling approach as for the primary non-inferiority analysis.

4.8.2   Analysis of secondary and exploratory variables

All secondary endpoints will be analysed using the Full Analysis set including values prior to rescue treatment or discontinuation. For HbA1c, weight, BMI and waist circumference, values recorded after rescue treatment for those patients who used rescue medication or values collected more than 8 days after the last dose date for patients who stayed more than 8 consecutive days off treatment are excluded from the analysis. For FPG, values recorded after rescue treatment for those patients who used rescue medication or values collected more than 1 day after the last dose date for patients who stayed more than 1 consecutive day off treatment are excluded from the analysis. For SBP, values recorded after rescue treatment for those patients who used rescue medication or values collected more than 4 days after the last dose date for patients who stayed more than 4 consecutive days off treatment are excluded from the analysis.

The statistical testing of the primary and key secondary efficacy variables will proceed in a sequential manner. If for the primary comparison between dapagliflozin or dapagliflozin plus saxagliptin (added to metformin) treatment group and the glimepiride (added to metformin) treatment group, the upper limit from a 2-sided 95% CI for the difference in adjusted means is less than 0.30%, then the dapagliflozin or dapagliflozin plus saxagliptin will be non-inferior to glimepiride and all four key secondary efficacy variables will be tested for superiority at a 0.05 level (two-sided) as well as the superiority test of the primary efficacy variable. To protect the type I error rate of the hierarchical testing procedure, the interpretation of the statistical significance of treatment comparisons for each key secondary efficacy variable and the superiority test of the primary efficacy variable will be done using a step-wise procedure (described in Section 4.3.1).

A summary of each efficacy variable and associated analysis is provided in Table 11.

The analysis of the changes from baseline to week 52 for a) total body weight, b) FPG and c) SBP will be performed using the MMRM model (as described for the primary efficacy endpoint). Point estimates and 2-sided 95% CI will be calculated for the adjusted mean changes from baseline within each treatment group and between treatment groups together with the p-values corresponding to testing the hypotheses of no difference between

dapagliflozin added to metformin and dapagliflozin plus saxagliptin added to metformin compared to glimepiride added to metformin.

The time spent below HbA1C target (<7% and <7.5%) from baseline to week 52 will be analysed using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and baseline HbA1c (see section 4.5.5). The change from baseline at week 52 in a) BMI and b) waist circumference will be analysed using an ANCOVA model with fixed effects for treatment groups and respective baseline covariates (see section 4.5.5). LOCF will be applied as detailed in section 4.6.2 for the latter two analyses. The ANCOVA model will be used to derive a least squares estimate of each test drug combination versus the control with 95% CI and (a corresponding 2-sided) p-value. In addition, a 2-sided 95% CI for the mean change within each treatment group will be calculated.

Time to rescue will be analysed using a Cox proportional hazards model with the Efron method (Ref 2) for handling ties (i.e., same rescue times). Estimates of the hazard ratio and 95% CI will be provided. Kaplan-Meier estimates will be calculated and plotted by treatment group. Median time to rescue and their 95% CIs (derived from the Kaplan-Meier estimates) will also be reported. Patients will be censored at the final visit (Visit 12; week 52) if rescue has not occurred by then (Section 4.5.6), or will be censored at the time of insulin start (for those subjects who received rescue treatment without confirmed rescue criteria). The proportional hazards (PH) assumption of the Cox model will be visually checked (e.g., the survival curves should not cross for the PH to hold). If the PH assumption is not met, the time to rescue will be analysed using a Wilcoxon test (using SAS proc lifetest).

The proportion of patients with at least one episode of confirmed hypoglycaemia, the proportion achieving HbA1c <7% (and <7.5%) without confirmed hypoglycaemia at week 52, the proportion achieving HbA1c <7% (and <7.5%) at week 52, the proportion achieving their individually agreed HbA1c targets at week 52, the proportion with at least one episode of any hypoglycaemia and the proportion with at least one episode of hypoglycaemia (symptomatic with blood glucose ≤70mg/dL [3.9mmol/L]) will be summarised by treatment group and compared between treatment groups using logistic regression with baseline HbA1c as a covariate (see section 4.5.7). The adjusted percentage with 95% CI, Odds Ratio with 95% CI and nominal p-values for the comparison of dapagliflozin or dapagliflozin plus saxagliptin vs glimepiride will be presented. The confidence intervals will be based on the profile likelihood method.

The proportion of patients achieving a ≥5% weight reduction or ≥5% weight gain will be summarised by treatment group and compared between treatment groups using logistic regression with baseline weight as a covariate.

The proportion of patients with an HbA1c decrease ≥1% with no weight gain at week 52 will be summarised by treatment group and comparisons between treatment groups (contrasts of each test combination vs the control) will be performed using a Pearson's Chi-Square test. Nominal p-values and asymptotic 95% CIs will be presented.

Descriptive summaries of change from baseline in HbA1c, FPG, weight, BMI, waist circumference and systolic BP over time (observed values), will be presented in addition to the analyses described above.

4.8.3   Exploratory Variables

The summaries described below will be based on the Full Analysis Set including values prior to rescue treatment or discontinuation. Values recorded after rescue treatment for those patients who used rescue medication or values collected more than 8 days after last dose date for patients who stayed more than 8 consecutive days off treatment are excluded from the analyses.

4.8.3.1   SF-36v2

The SF-36v2 questionnaire contains 36 items and covers 8 health domain scales and 2 psychometrically based physical and mental component summary measures. The 8 health domain scales are referred to as follows: physical functioning (PF); role - physical (RP); bodily pain (BP); general health (GH); vitality (VT); social functioning (SF); role - emotional (RE); mental health (MH). The 2 summary measures are referred to as the physical component score (PCS) and mental component score (MCS).

Standardised scores will be generated using the validated scoring software package (QualityMetric Health Outcomes^{TM} Scoring Software 4.5 (or later version)) for the 8 health domain scales and 2 summary measures using the raw data entered in the eCRFs.

The scores for each of the 8 health domain scales along with the PCS and MCS summary measures will be summarised by absolute values and changes from baseline at week 24 and week 52.

4.8.3.2   HFS II – Worry subscale

A mean summary score will be calculated by summing the responses to the 18 questions and dividing by the number of answered questions. If < 50% of the questions are answered, the mean score will not be calculated. Absolute values and changes from baseline in this mean score will be summarised by treatment group at week 24 and week 52.

4.8.3.3   IWQOL-Lite

A score for each of the 5 domains (physical function, self-esteem, sexual-life, public distress and work) and a total score will be calculated as detailed in Appendix V. The raw scores will be converted to transformed scores (ranging from 0 to 100) as described in Appendix V. Absolute values and change from baseline in the transformed scores will be summarised by treatment group at week 24 and week 52.

4.8.3.4   Waist:Hip ratio

Change from baseline in waist:hip ratio will be summarised at week 52.

4.8.4 Sensitivity analysis

To assess the robustness of the primary efficacy results, sensitivity analyses will be carried out as follows for change from baseline in HbA1c to week 52:

- The primary MMRM model will be repeated using the Per-Protocol analysis set
- An ANCOVA analysis will be performed using values prior to rescue treatment at week 52. If the Week 52 value is missing or post rescue treatment/discontinuation, the last post-baseline measurement prior to week 52 and prior to rescue treatment will be used.
- The primary MMRM model will be repeated including all values according to the ITT principle (i.e. all values will be included regardless of use of rescue treatment or treatment discontinuation)

In addition, as noted in section 4.6.2, summaries of missing data by visit will be used to assess the missing data assumptions (See example in Table 16 in Appendix IV). A spaghetti plot to show drop-out patterns over time will also be provided.

4.8.5 Subgroup analyses

The primary efficacy analysis will be repeated to summarize HbA1c within subgroups based on: age group (<65, ≥65 - <75, ≥75 yrs), gender, female age group (≤50, >50 yrs), race, country, baseline HbA1c ($<8\%$, $\geq8\%$ - $<9\%$, $\geq9\%$), and baseline eGFR (<30, ≥30 - <45, ≥45 - <60, ≥60 - <90, ≥90 mL/min/1.73m^2). The primary MMRM model will be repeated as described in Section 4.5.4.3. The nominal p-value for the subgroup-by-treatment interaction at week 52 will be presented.

If the value of the grouping variable cannot be determined, the patient will be excluded from the corresponding subgroup analysis. For each subgroup analysis, if, in any treatment group, the number of patients is less than 10 for a subgroup, this subgroup will not be included in the interaction model and descriptive summaries only will be displayed. If there are problems with the convergence of the MMRM model, descriptive summaries within subgroups will be provided.

4.9 Safety analysis

All safety analyses will be performed on the Safety Analysis Set. Summaries of safety data will be produced for the double-blind (DB) treatment period (on-treatment) only, while listings will include all events, i.e., listings will include values during the pre-treatment period, during the DB treatment period and during the follow-up period.

A separate page to capture events of hypoglycaemia is contained within the CRF (AZ module HYPOE). Hypoglycaemia (or discontinuation due to hypoglycaemia) will not be reported on an AE CRF page unless the event fulfilled criteria for SAE (in which case a SAE form will be completed). Hypoglycaemia events that are reported as SAEs will be included in all

summaries of AEs or SAEs. Separate summaries will be provided including hypoglycaemia events reported on that special CRF page (see Section 4.9.6).

Analysis of changes from baseline to a specific time point (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 unless otherwise specified.

SAEs and the lab measurements for the liver function tests will be included in the summaries only if they occurred or were measured on or prior to the 30th day after the last blinded drug treatment date. All other safety events (non-severe AEs, hypoglycaemia, etc.) and measurements (safety labs, vital signs etc.) will be included in the summaries only if they occurred or were measured on or prior to the 4th day after the last blinded drug treatment date.

No formal statistical testing will be performed for safety analyses; only descriptive summaries will be provided. A dot plot (showing relative risk) will be produced for the most common adverse events.

4.9.1   Adverse events

Adverse events will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the MedDRA (version 19.1 or later). Summaries of AEs will be produced by SOC, PT and treatment group. In summaries by SOC and PT, AEs will be sorted by decreasing frequency within each SOC and PT according to the dapagliflozin + metformin dose group. In summaries by PT, AEs will be sorted by decreasing frequency within PT according to the dapagliflozin + metformin dose group.

Summaries of AEs will report the number (and percentage of patients) of the following:

- All AEs (including AEs, SAEs, death, hypoglycaemia, treatment-related events and events leading to the discontinuation of study medication)
    - a) using data obtained prior to rescue medication only
    - b) repeated to contain all data regardless of use of rescue medication
- AEs by SOC and PT
    - a) using data obtained prior to rescue medication only
    - b) using all data regardless of use of rescue medication

The following summaries will be provided using all data regardless of use of rescue medication:

- AEs by SOC and PT by age categories
- AEs by SOC and PT by gender
- AEs by SOC and PT by female age categories
- AEs by SOC and PT by race
- Most common AEs (i.e., occurring in at least 2% of patients in any treatment group) by PT
- AEs by SOC, PT and intensity

- Treatment-related AEs by SOC and PT
- Most common AEs (i.e., occurring in at least 5% of patients in any treatment group) by PT

AEs will be summarised for the double-blind treatment period only; listings of AEs will include all events throughout the study period (i.e. pre-treatment period, double-blind treatment period and follow-up).

A dot plot (showing relative risk) will be produced for the most common adverse events (by preferred term).

4.9.2 Serious adverse events

All serious adverse events (SAEs) will be described in narratives, regardless of investigator assessment of causality.

Summaries of SAEs will be produced for the double-blind treatment period (using all data regardless of use of rescue medication) and will consist of:

- SAEs by SOC and PT
- SAEs related to study medication by SOC and PT

Listings of SAEs will include all events throughout the study period i.e. pre-treatment period, double-blind treatment period and follow-up.

4.9.3 Adverse events leading to discontinuation of study medication

AEs with an onset during the double-blind treatment period reported with an action taken of permanent discontinuation of study medication will be summarised by SOC and PT (using all data regardless of use of rescue medication). This summary will include hypoglycaemia events that were reported as SAEs.

In addition to a narrative description, a patient listing of discontinuation due to AEs will be provided - displaying all events that led to discontinuation of study medication with an onset date prior to the double-blind treatment period and up to the follow-up period, if any.

4.9.4 Adverse events of special interest

Adverse events of special interest (AEOSI) will be defined based on lists of preferred terms. These lists will be reviewed and finalized prior to database lock and unblinding of the database.

The following summaries and listings of AEOSI will include all data regardless of use of rescue medication:

- AEs of genital infection
- AEs of genital infection by gender

- AE of antimicrobial treatment for genital infection by gender
- AEs of Urinary Tract Infection (UTI)
- AEs of UTI by gender
- AEs of antimicrobial treatment for UTI by gender
- AEs of renal impairment/failure
- AEs of volume depletion
- AEs of fracture
- AEs of hepatic disorder
- AEs of hypersensitivity reactions
- AEs of severe cutaneous adverse reactions
- AEs of gastroenteritis and upper respiratory tract infections
- AEs of decreased lymphocyte count
- AEs of pancreatitis
- AEs of all malignancies
- AEs of confirmed adjudicated hospitalisations for cardiac failure events
- AEs of cardiac failure
- AEs of DKA

Details of the summaries to be provided for events of Hypoglycaemia can be found in Section 4.9.6.

4.9.5   Deaths

All deaths recorded on the AE page 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. Deaths with an onset from day 1 of the double-blind treatment period up to and including 30 days after the last dose date will be considered as occurring during the double-blind treatment period.

Summaries of deaths will include data regardless of use of rescue medication; listing of deaths will also include all data regardless of use of rescue medication (Enrolled population).

4.9.6   Hypoglycaemia

Hypoglycaemic events occurring after the start of double blind study medication up to and including 4 days after the last double-blind dosing date will be considered as obtained during the double-blind treatment period and included in the summaries described below.

The proportion of patients with hypoglycaemic events and the number of hypoglycaemic events per patient will be summarised by treatment group. Hypoglycaemic events will also be categorised as follows:

- <u>Major hypoglycaemic events:</u> symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose

value <54 mg/dL (<3.0 mmol/L), and prompt recovery after glucose or glucagon administration

- Hypoglycaemia: Typical symptoms of hypoglycaemia accompanied by blood glucose ≤70 mg/dL (3.9 mmol/L)
- Other episodes of hypoglycaemia: Symptoms of hypoglycaemia without a blood glucose reading or symptoms of hypoglycaemia accompanied by blood glucose >70 mg/dL (3.9 mmol/L)
- Confirmed hypoglycaemia: Typical symptoms of hypoglycaemia accompanied by blood glucose ≤50 mg/dL (2.8 mmol/L)
- Asymptomatic hypoglycaemia: An event not accompanied by typical hypoglycaemia symptoms but with measured plasma glucose ≤70 mg/dL (≤3.9 mmol/L)

Hypoglycaemic events leading to discontinuation of study medication will be summarised by treatment. A summary of hypoglycaemic events over time by treatment will also be provided.

Summaries will be produced using data obtained prior to rescue medication only then repeated using all data regardless of use of rescue medication for patients in the Safety Analysis Set. A listing of patients will be produced for all hypoglycaemic events.

4.9.7   Laboratory evaluation

Unless otherwise specified, laboratory data obtained after the start of study medication and up to and including 4 days (or 30 days for liver function laboratory test) after the last dose of the double-blind treatment period, will be considered as obtained during the double-blind treatment period.

Laboratory data (including haematology, clinical chemistry, creatinine and lipids; Appendix III) will be summarised by visit using the analysis windows defined in Table 12. Values and changes from baseline for laboratory data will be summarised by treatment group at each scheduled visit during the double blind treatment period using descriptive statistics (using all available data regardless of use of rescue medication) for patients in Safety Analysis Data Set. Summaries of laboratory data will be produced for the double-blind treatment period, while listings will include values from the follow-up visit.

4.9.7.1   Marked laboratory abnormalities

Laboratory abnormalities will be evaluated based on marked abnormality values (MA). The pre-defined criteria for marked abnormalities are detailed in Appendix III, Table 15. If both the baseline and on-treatment values of a parameter are beyond the same MA limit for the parameter, then the on-treatment value will be considered an MA only if it is more extreme (farther from the limit) than was the baseline value. If the baseline value is beyond the low MA limit, and the post-baseline value is beyond the high MA limit (or vice-versa), then the post-baseline value will be considered a MA.

Laboratory abnormalities during the double-blind treatment period will be summarised using all data regardless of use of rescue medication.

Additionally, patients with MA will be listed.

4.9.7.2   Additional laboratory data summaries

Shift tables will be produced for the following parameters (including all data regardless of use of rescue medication):

- Sodium, calcium, phosphorus and magnesium baseline to highest category of Low, Normal or High
- Sodium, potassium and calcium baseline to lowest category of Low, Normal or High
- Urinary Albumin to Creatinine Ratio (UACR) for categories of albuminuria (normal (0-<30mg/g), micro(30-,300 mg/g), macro($\geq$ 300 mg/g))

For liver safety, a summary of the proportion of patients with elevated liver tests including elevated AT (ALT and/or) AST) and total bilirubin will be provided. The following three criteria will be summarised:

- (AST or ALT > 3XULN) and (Bilirubin > 1.5XULN within 14 days on or after AT elevation)
- (AST or ALT > 3XULN) and (Bilirubin > 2XULN within 14 days on or after AT elevation)
- (AST or ALT > 3XULN) and {(Bilirubin > 2XULN and no ALP >= 2XULN) within 14 days on or after AT elevation)}

4.9.8   Vital signs

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

Vital sign measurements include systolic and diastolic blood pressure and pulse are measured with the patient in a sitting position.

Vital signs data will be summarised by visit using the visit windows defined in Table 12. Values and changes from baseline for vital sign measurements will be summarised by treatment group at each scheduled visit during the double-blind treatment period using descriptive statistics (using all available data regardless of use of rescue medication) for patients in Safety Analysis Data Set.

4.9.9   Electrocardiograms

The normality/abnormality of the ECG tracing (as determined by the investigator) will be summarised using frequency tables on number of patients with a normal/abnormal ECG

tracing at baseline versus week 52 of the double-blind treatment period. When the data at week 52 is not available for a patient, the last observation prior to week 52 of that patient will be used in the summary.

A listing of patients will be produced which will display all ECG findings up to week 52 in patients with abnormal ECGs (as determined by the investigator).

4.9.10   Pregnancy test results

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

4.10   Figures and graphs

The following figures will be presented by treatment group.

- Longitudinal plots
  - HbA1c adjusted mean change from baseline over time
  - Total body weight adjusted mean change from baseline over time
  - FPG adjusted mean change from baseline over time
- Forest plots
  - HbA1c adjusted mean change from baseline to week 52
  - Total body weight adjusted mean change from baseline to week 52
  - Proportion of patients reporting at least one episode of confirmed hypoglycaemia from baseline until week 52
- Kaplan-Meier curves for:
  - Time to rescue
  - Time to discontinuation of study medication
- Spaghetti plot
  - Mean HbA1c over time grouped by last available visit on treatment
- Dot plot (showing relative risk) for:
  - Most common Adverse Events, by preferred term

4.11   Conventions

4.11.1   Study Day

If the date of assessment is prior to first dose of study medication then study day will be calculated as:

Study day = Date of assessment – Date of first dosing.

If the date of assessment is on or after the day of first dose then study day will be calculated as:

Study day = Date of assessment – Date of first dosing + 1

Day 1 of the double-blind treatment period is the start date of double-blind study medication.

4.11.2   Visit Windows

Deviations are to be expected between patients in the actual number of study days from randomisation to when planned visits are carried out. To handle these deviations in tables, figures, listings, and analyses, visit assessments will be slotted according to visit windows. Data will be assigned to the visit windows using study day. For the efficacy and safety data, the data will be listed and summarised by visit as listed in Table 12 below:

Table 12. Visit windows for efficacy and safety data

Visit	Target Day	Adjusted windows for analyses (Days)			
		HbA1c	Vital Signs, sBP Body Weight, FPG*, urinalysis hypoglycaemic events	Waist circumference, BMI, ECG, complete physical examination**	Laboratory parameters***, Serum lipids
Baseline	1	≤1	≤1	≤1	≤1
Week 2	15	2 - 21	2 - 21		
Week 4	29	22 - 35	22 - 35		
Week 6	43	36 - 49	36 - 49		
Week 8	57	50 - 63	50 - 63		
Week 10	71	64 - 77	64 - 77		
Week 12	85	78 - 126	78 - 126		
Week 24	169	127 - 210	127 - 210		
Week 36	253	211 - 294	211 - 294		
Week 48	337	295 - 348	295 - 348		
Week 52	365	349 - Last dosing date[¥] + 7	349 - Last dosing date[¥] + 4*	2 – Last dosing date of the DB period + 4	2 – Last dosing date of the DB period + 4
Follow-up Week 55	386	(Last dosing date[¥] + 7) – Last visit date	(Last dosing date[¥] + 4*) – Last visit date		(Last dosing date[¥] + 4) – Last visit date

*: For FPG, week 52 and week 55 windows use last dosing date +1.

**: also assessed at Week 24; **: clinical chemistry parameters also assessed at Weeks 12, 24, 36, 48.

[¥]: Last dosing date ≥ Day 349

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 non-missing observation closest to the target day will be used in the analysis
- If two observations are equidistant from the target day, the non-missing observation with the later collection date will be used in the analysis
- If two observations are collected on the same day and have a collection time associated with them, the non-missing observation with the later collection 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 a visit window does not contain any observations, the data will be missing for that visit.

4.11.3 Post-Dosing Observations

While double blind treatment period efficacy and safety observations will be listed regardless of whether the patient was taking blinded study drug, observations will be summarised only when the following rules are satisfied:

For efficacy parameters

- HbA1C, body weight, BMI and waist circumference will be summarised only if measured on or before the 8th day after the last double-blind drug dosing date.
- FPG, will be summarised only if measured on or before the first day after the last randomised, double-blind drug dose date.
- SBP will be summarised only if measured on or before the 4th day after the last double-blind drug dosing date.

For safety parameters

- SAEs and the lab measurements for the liver function tests will be included in the summaries only if occurred/measured on or prior to the 30th day after the last blinded drug treatment date.
- All other safety events (non-severe AEs, hypoglycaemia, etc.) and measurements (safety lab, vital signs, etc.) will be included in the summaries only if occurred/measured on or prior to the 4th day after the last blinded drug treatment date.

4.11.4 Duration of Type 2 Diabetes and Missing Dates

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

(1 + consent date - diagnosis date) / 365.25

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 (provided that the imputed date is less than the consent date).
- 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.

These durations, even if partially imputed, will be listed. However, only the portion of the date of diagnosis actually observed, rather than imputed dates, will be displayed in listings.

4.11.5   Missing Dates for Adverse Events

If missing or partial dates of AE onset occur, a conservative approach will be followed and events will be assumed to be during the Double-Blind treatment period unless there is convincing evidence to the contrary. For AEs, a missing or incomplete onset date will be imputed according to the following conventions:

- 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 (pre-treatment, during DB treatment or follow-up). This derived date will not be reported in summary tables or listings. 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.

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

- If an onset date is incomplete, the derived onset date will be calculated using the following algorithm:
  o Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence):
    – First active study medication 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.

- o 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.
- o 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.
- o 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.

4.11.6   Counting Rules for Adverse Events

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.

Where a patient has multiple adverse events within the same system organ class in a single analysis period, the patient will only be counted once at the system organ class level in adverse event frequency tables.

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:** Earlier onset date events will take precedence over later onset date-time events in determining the event to include in summary.

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

4.11.7   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 ($>$, $\geq$, $<$, or $\leq$), 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.

5.   CHANGES OF ANALYSIS FROM THE PROTOCOL

1. The protocol text for the analysis of the primary efficacy variable specifies the null and alternative hypotheses in terms of 'control minus test' as follows:

The null hypothesis H_0 (given below) will be tested against the alternative hypothesis H_A ($\alpha = 0.025$, one-sided):

H_0: $\mu_c - \mu_t \leq -0.30\%$,
H_A: $\mu_c - \mu_t > -0.30\%$

If the observed lower limit from a 2-sided 95% (or 1-sided 97.5%) CI for the difference in adjusted means is greater than -0.30%, then the test group will be considered to be non-inferior to the control group.

In order to be consistent with previous AZ studies of this nature and to aid comparisons across studies, this SAP refers to this in terms of 'test minus control' as follows:

The null hypothesis H_0 (given below) will be tested against the alternative hypothesis H_A ($\alpha = 0.025$, one-sided):

H_0: $\mu_t - \mu_c \geq 0.30\%$,
H_A: $\mu_t - \mu_c < 0.30\%$

If the upper limit of the 2-sided 95% CI is less than 0.30% then dapagliflozin or dapagliflozin plus saxagliptin will be considered to be non-inferior to glimepiride.

6. REFERENCES

1. The prevention and treatment of missing data in clinical trials. Washington, DC: National Academies Press. National Research Council 2010
2. Efron B. The efficacy of Cox's Likelihood function for censored data. Journal of the American Statistical Association. 1977; 72, 557-565.

7. APPENDICES

7.1 Appendix I

7.1.1 List of Planned Tables

Demography
1. Patient disposition (All patients)
2. Analysis sets (All patients)
3. Relevant protocol deviations (Full analysis set)
4. Demographic characteristics (Randomised patients set)
5. Patient characteristics (Randomised patients set)
6. Diabetes-related and renal baseline characteristics (Randomised patients set)
7. Patient recruitment by country and centre (Randomised patients set)
8. Diabetes-related disease history (Randomised patients set)
9. Medical and surgical history (Randomised patients set)
10. All current medications (Safety analysis set)
11. All concomitant medications (Safety analysis set)

Extent of Exposure
12. Extent of exposure to Investigational Product (Safety analysis set)
13. Metformin dose at randomisation (Safety analysis set)
14. Dose levels of Glimepiride (Safety analysis set)
15. Dose levels of Glimepiride over time (Safety analysis set)
16. Dose titrations of Glimepiride (Safety analysis set)
17. Treatment interruptions (Safety analysis set)
18. Study treatment compliance (Safety analysis set)

Efficacy
19. Primary efficacy endpoint - change from baseline in HbA1c at week 52 (Full analysis set)
20. Key Secondary efficacy endpoints (Full analysis set)
21. Change from baseline in HbA1c - MMRM summary over time (Full analysis set)
22. Sensitivity analysis - change from baseline in HbA1c at week 52 (Per Protocol analysis set)
23. Sensitivity analysis - change from baseline in HbA1c at week 52, LOCF ANCOVA (Full analysis set)
24. Sensitivity analysis - change from baseline in HbA1c at week 52 including all values regardless of use of rescue treatment or treatment discontinuation (Full analysis set)
25. Change from baseline in HbA1c - Assessment of missing data patterns (Full analysis set)
26. Primary efficacy analysis - MMRM summary (Full analysis set)
27. Change from baseline in HbA1c at week 52 by baseline HbA1c (Full analysis set)
28. Change from baseline in HbA1c at week 52 by age (Full analysis set)
29. Change from baseline in HbA1c at week 52 by gender (Full analysis set)
30. Change from baseline in HbA1c at week 52 by female age group (Full analysis set)
31. Change from baseline in HbA1c at week 52 by race (Full analysis set)
32. Change from baseline in HbA1c at week 52 by country (Full analysis set)

33. Change from baseline in HbA1c at week 52 by baseline eGFR (Full analysis set)
34. Change from baseline in weight - MMRM summary over time (Full analysis set)
35. Change from baseline in FPG - MMRM summary over time (Full analysis set)
36. Time to rescue - Kaplan Meier estimates (Full analysis set)
37. Proportion meeting HbA1c criteria without confirmed hypoglycaemia at week 52 (Full analysis set)
38. Proportion meeting HbA1c criteria at week 52 (Full analysis set)
39. Proportion achieving individually agreed HbA1c targets at week 52 (Full analysis set)
40. Proportion with a HbA1c decrease >=1% with no weight gain (Full analysis set)
41. Time spent below HbA1c target (<7% and <7.5%) (Full analysis set)
42. Change in BMI from baseline to week 52 (LOCF) (Full analysis set)
43. Proportion with a weight reduction >=5% or a weight gain >=5% (Full analysis set)
44. Proportion with at least 1 episode of any hypoglycaemia (Full analysis set)
45. Change in waist circumference from baseline to week 52 (LOCF) (Full analysis set)
46. Change in systolic blood pressure from baseline to week 52 (MMRM) (Full analysis set)
47. Proportion with at least one episode of hypoglycaemia (symptomatic + blood glucose ≤70 mg/dL [3.9 mmol/L]) (Full analysis set)
48. Change from baseline over time in efficacy variables (observed values) (Full analysis set)

Exploratory
49. SF-36v2 scores and change from baseline (Full analysis set)
50. HFS-II worry scale - mean score and change from baseline (Full analysis set)
51. IWQOL-Lite scores and change from baseline (Full analysis set)
52. Waist-to-hip ratio (Full analysis set)

Adverse Events
53. Overall adverse events summary (Safety analysis set) - with data prior to rescue treatment only
54. Overall adverse events summary (Safety analysis set) - including all data regardless of rescue
55. Adverse events by SOC and PT (Safety analysis set) - with data prior to rescue treatment only
56. Adverse events by SOC and PT (Safety analysis set) - including all data regardless of rescue
57. Adverse events by SOC and PT by age categories (Safety analysis set) - including all data regardless of rescue
58. Adverse events by SOC and PT by gender (Safety analysis set) - including all data regardless of rescue
59. Adverse events by SOC and PT by female age categories (Safety analysis set) - including all data regardless of rescue
60. Adverse events by SOC and PT by race (Safety analysis set) - including all data regardless of rescue
61. Most common adverse events (frequency >=5% in any treatment group) (Safety analysis set) - including all data regardless of rescue

62. Most common adverse events (frequency >=2% in any treatment group) (Safety analysis set) - including all data regardless of rescue

63. Adverse events by SOC and PT by maximum intensity (Safety analysis set) - including all data regardless of rescue

64. Causally related Adverse events by SOC and PT (Safety analysis set) - including all data regardless of rescue

65. Adverse events with an outcome of death by SOC and PT (Safety analysis set) - including all data regardless of rescue

66. Adverse events with outcome of death - key patient information (Safety analysis set) - including all data regardless of rescue

67. Serious adverse events by SOC and PT (Safety analysis set) - including all data regardless of rescue

68. Serious adverse events causally related to study medication by SOC and PT (Safety analysis set) – including all data regardless of rescue

69. Adverse events leading to discontinuation of study medication by SOC and PT (Safety analysis set) – including all data regardless of rescue

70. Adverse events of special interest, preferred terms

71. Adverse events of special interest, genital infection (Safety analysis set)

72. Adverse events of special interest, genital infection by gender (Safety analysis set)

73. Adverse events of special interest, antimicrobial treatment for genital infection by gender (Safety analysis set)

74. Adverse events of special interest, urinary tract infection (Safety analysis set)

75. Adverse events of special interest, urinary tract infection by gender (Safety analysis set)

76. Adverse events of special interest, antimicrobial treatment for urinary tract infection by gender (Safety analysis set)

77. Adverse events of special interest, renal impairment/failure (Safety analysis set)

78. Adverse events of special interest, volume depletion (Safety analysis set)

79. Adverse events of special interest, fracture (Safety analysis set)

80. Adverse events of special interest, hepatic disorder (Safety analysis set)

81. Adverse events of special interest, hypersensitivity reactions (Safety analysis set)

82. Adverse events of special interest, severe cutaneous adverse reactions (Safety analysis set)

83. Adverse events of special interest, gastroenteritis and upper respiratory tract infections (Safety analysis set)

84. Adverse events of special interest, decreased lymphocyte count (Safety analysis set)

85. Adverse events of special interest, pancreatitis (Safety analysis set)

86. Adverse events of special interest, all malignancies (Safety analysis set)

87. Adverse events of special interest, confirmed adjudicated hospitalisations for cardiac failure events (Safety analysis set)

88. Adverse events of special interest, cardiac failure (Safety analysis set)

89. Adverse events of special interest, DKA (Safety analysis set)

90. Non-serious adverse events occurring in greater than 5% of patients (Safety analysis set)

91. Hypoglycaemic events (Safety analysis set) - with data prior to rescue treatment only

92. Hypoglycaemic events (Safety analysis set) - including all data regardless of rescue

93. Hypoglycaemic events over time (Safety analysis set) - with data prior to rescue treatment only

94. Hypoglycaemic events over time (Safety analysis set) - including all data regardless of rescue

Laboratory Data, Vital Signs and ECG

95. Haematology and clinical chemistry laboratory variables over time (Safety analysis set)

96. Lipid parameters over time (Safety analysis set)

97. Marked Laboratory Abnormalities (Safety analysis set)

98. Proportion of subjects with elevated liver tests (Safety analysis set)

99. Patients with combined ALT or AST, and bilirubin, elevations - individual patient data (Safety analysis set)

100. Sodium, Calcium Phosphorous and Magnesium, baseline to maximum value during treatment (Safety analysis set)

101. Sodium, Calcium Phosphorous and Magnesium, baseline to minimum value during treatment (Safety analysis set)

102. Urine Albumin to Creatinine Ratio shift table Baseline to Week 52 value (Safety analysis set

103. Urinalysis, baseline versus maximum value on treatment, shift table (Safety analysis set)

104. Vital signs variables over time (Safety analysis set)

105. ECG baseline versus week 52 (Safety analysis set)

7.1.2   List of Planned Figures

1. HbA1c - adjusted mean change from baseline over time (Full analysis set)
2. Weight - adjusted mean change from baseline over time (Full analysis set)
3. FPG - adjusted mean change from baseline over time (Full analysis set)
4. HbA1c - difference in adjusted mean change from baseline to week 52, Forest Plot (Full analysis set)
5. Weight - difference in adjusted mean change from baseline to week 52, Forest Plot (Full analysis set)
6. Proportion of patients reporting at least one episode of confirmed hypoglycaemia from baseline to week 52, Forest Plot (Full analysis set)
7. Kaplan-Meier plot of Time to rescue(Full analysis set)
8. Kaplan-Meier plot of Time to discontinuation of study medication (Full analysis set)
9. HbA1c - adjusted mean change from baseline over time by baseline HbA1c (Full analysis set)
10. Spaghetti plot of mean HbA1c over time (observed) grouped by last available visit on treatment – Excluding data after rescue (Full analysis set)
11. Most common adverse events (>=2%), by preferred term, dot plot showing relative risk (Safety analysis set)

7.1.3 List of Planned Listings

1. Study medication batch numbers
2. Randomisation scheme and codes (Randomised patients set)
3. Patient disposition I (Enrolled patients)
4. Patient disposition II (Randomised patients set)
5. Relevant protocol deviations (Full analysis set)
6. Analysis sets
7. Exclusions from analysis sets
8. Demographic Characteristics (Randomised patients)
9. Baseline characteristics (Randomised patients)
10. Medical and surgical history (Randomised patients set)
11. All current medications (Safety analysis set)
12. All concomitant medications (Safety analysis set)
13. Metformin treatment details (Safety analysis set)
14. Insulin Treatment details (Safety analysis set)
15. Study Drug Accountability (Safety analysis set)
16. Exposure Data (Safety analysis set)
17. Titration data (Safety analysis set)
18. Efficacy parameters over time (Full analysis set)
19. Efficacy parameters I (Full analysis set)
20. Efficacy parameters II (Full analysis set)
21. SF-36 raw data (Full analysis set)
22. SF-36 derived data (Full analysis set)
23. HFS-II Worry Scale (Full analysis set)
24. IWQOL-Lite raw data (Full analysis set)
25. IWQOL-Lite derived data (Full analysis set)
26. Adverse Events (Safety analysis set)
27. Serious adverse events (Safety analysis set)
28. Adverse Events leading to discontinuation of study medication (Safety analysis set)
29. Adverse Events of special interest (Safety analysis set)
30. Events of hypoglycaemia I (Safety analysis set)
31. Events of hypoglycaemia II (Safety analysis set)
32. Laboratory data (Safety analysis set)
33. Marked Laboratory Abnormalities data (Safety analysis set)
34. Liver Function Tests (Safety analysis set)
35. Vital Signs (Safety analysis set)
36. Abnormal ECG Findings (Safety analysis set)
37. Pregnancy Data (Safety analysis set)

7.2   Appendix II – Inclusion and Exclusion Criteria

Table 13. Patient inclusion and exclusion criteria

Inclusion criteria

1.   Provision of informed consent prior to any study-specific procedures
 	
2.   Is able to read, understand, and sign the Informed Consent Forms (ICFs) and, if applicable, an Authorisation to Use and Disclose Protected Health Information form, communicate with the Investigator, understand and comply with protocol requirements (including the use of diary and glucose meter measurements)
 	
3.   Is male or female of ≥18 and <75 years old at time of informed consent
 	
4.   Has a documented diagnosis of T2DM
 	
5.   Has a HbA1c of ≥7.5% and ≤10.5% based on central laboratory results from Visit 1, with individual need for therapy escalation
 	
6.   Currently treated with a stable MTD (≥1500 mg/day) of metformin therapy for at least 8 weeks prior to Enrolment visit
 	
7.   Has a BMI of ≤45 kg/m^2 at enrolment visit
 	
8.   Has a C-peptide laboratory value of ≥1.0 ng/mL (0.33 nmol/L; 333.3 pmol/L) based on central laboratory results from Visit 1
 	
9.   For females only: women not of childbearing potential, or if they are women of childbearing potential (WOCBP), they must comply with the following:
 	
    o   Are not pregnant or breastfeeding
 	
    o   Have a negative urine pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin, beta subunit [βhCG]) at Visit 1 (Enrolment) and prior to randomisation.
 	
    o   Using or willing to adopt a highly effective method of birth control to avoid pregnancy throughout the study and for at least 4 weeks after the last dosing of study medication

Exclusion criteria
1.   Clinically diagnosed with Type I diabetes, known diagnosis of maturity onset diabetes of the young (MODY), or secondary diabetes mellitus or known presence of glutamate decarboxylase 65 (GAD65) antibodies 2.   History of diabetic ketoacidosis, hyperosmolar nonketotic coma, or corticosteroid induced Type 2 diabetes 3.   Symptoms of poorly controlled diabetes including, but not limited to, marked polyuria, polydipsia, and/or greater than 10% weight loss during the 3 months prior to Enrolment

4. FPG >270 mg/dL (>15 mmol/L) – assessed based on central laboratory results from Visits 1

5. History of diabetes insipidus

6. Patients with clinically significant thyroid disease or uncontrolled thyroid disease needing initiation or adjustment of thyroid treatment per Investigator's judgement. Abnormal thyroid stimulating hormone (TSH) value at Enrolment will be further evaluated by free thyroxine (T4). Patients with abnormal free T4 values will be excluded

7. History of bariatric surgery or lap-band surgery, or either procedure is planned during the time period of the study. History of liposuction is allowed.

8. History of any unstable endocrine, psychiatric, rapidly progressing or unstable renal disease, or rheumatic disorder, as judged by the Investigator.

9. Patients who, in the judgment of the Investigator, may be at risk for dehydration or volume depletion that may affect the patient's safety and/or the interpretation of efficacy or safety data

10. Has evidence of current abuse of drugs or alcohol or a history of abuse within the past 52 weeks that, in the Investigator's opinion, would cause the individual to be noncompliant

11. Clinically significant cardiovascular disease or procedure within 3 months prior to Enrolment (ie, MI, cardiac surgery, coronary artery bypass surgery, coronary stent placement, coronary angioplasty, unstable angina, stroke, transient ischaemic attack, or unstable or previously undiagnosed arrhythmia) or expected to require coronary revascularization procedure during the course of the study

12. Severe uncontrolled hypertension defined as systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg at any visit up to and including Randomization (Visit 2)

13. Presence or history of severe congestive heart failure (New York Heart Association Class III and IV [CCNYHA 1994]), unstable or acute congestive heart failure, and/or known left ventricular ejection fraction of ≤40%

14. Creatinine clearance (CrCl) of <60 mL/min based on central laboratory results from Visit 1

15. Familial renal glucosuria. This condition is diagnosed as glucosuria (>1.0 mmol/L urine) in the presence of normoglycaemia in patients without the diagnosis of diabetes mellitus

16. Significant hepatic disease, including, but not limited to, severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) of >3x upper limit of normal (ULN) based on central laboratory results from Visit 1

17. Serum total bilirubin (TB) of >2 mg/dL (34.2 μmol/L [patients with documented Gilbert's syndrome will be allowed to enrol]) based on central laboratory results from Visit 1

18. History of, or currently have, acute or chronic pancreatitis or have triglyceride concentrations ≥500 mg/dL based on central laboratory results from Visit 1.

19. History of severe hepatobiliary disease or hepatotoxicity with any medication

20. Positive serologic evidence of current infectious liver disease, including patients positive for

Hepatitis B viral antibody IgM, Hepatitis B surface antigen, and Hepatitis C virus antibody

21. History of malignancy within 5 years of Visit 1 (Enrolment), with the exception of treated in situ basal cell or squamous cell carcinoma of the skin

22. Haemoglobin <10 g/dL (<100 g/L) or 6.2 mmol/L for men; haemoglobin <9.0 g/dL (<90 g/L) or 5.9 mmol/L for women

23. History of chronic haemolytic anaemia or haemoglobinopathies (for example, sickle cell anaemia, thalassemia, sideroblastic anaemia). Mild haemolysis due to artificial heart valves or due to sickle cell trait is not an exclusion criterion except when haemoglobin levels are too low (as defined in haemoglobin criteria above)

24. Donation or transfusion of blood, plasma, or platelets within the past 12 weeks prior to Enrolment, or planning to donate blood during the study

25. Concomitant treatment with loop diuretics at Visit 2 (Randomisation/baseline.

26. Administration of any antihyperglycaemic therapy, other than metformin, during the 8 weeks prior to Visit 1 (Enrolment)

27. Administration of any other IP or participation in any interventional clinical studies 30 days prior to Visit 1 (Enrolment)

28. Treatment with systemic glucocorticoids equivalent to oral prednisolone ≥10 mg (betamethasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day for >7 days within 30 days prior to enrolment

29. Prescription or over-the-counter weight loss medications within 3 months prior to Visit 1 (Enrolment)

30. Has a clinically significant medical condition that could potentially affect study participation and compliance with the treatment and study procedures, or which may pose a significant risk to the patient and/or personal well-being, as judged by the Investigator

31. Has clinically significant abnormality identified on physical examination, ECG, or laboratory tests (clinical chemistry, haematology, and urinalysis) as judged by the Investigator at Visit 1 (Enrolment) would compromise the patient's safety or successful participation in the clinical study

32. Has known contraindications, allergies, or hypersensitivities to any study drug or excipient as outlined in the IBs or local package inserts for metformin, SU, saxagliptin, and dapagliflozin

33. Ongoing weight loss more than 5% over the last 3 months prior to Visit 1 (Enrolment)

34. Known immunocompromised status, including patients who underwent organ transplantation

35. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff and/or staff at the study site)

36. Previous screening, enrolment or randomisation in the present study

7.3 Appendix III – Laboratory Parameters and Marked Abnormalities

Table 14. Laboratory parameters

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Red blood cell count	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total (TB)
B-Haemoglobin (Hb)	S/P-Alkaline phosphatase (ALP)
B-Haematocrit	S/P-Aspartate transaminase (AST)
B-Platelet count	S/P-Alanine transaminase (ALT)
	S/P-Uric acid
	S/P-Potassium
	S/P-Calcium, total
	S/P-Sodium
	S/P-Chloride
	S/P-Bicarbonate
	S/P-Magnesium
	S/P-Phosphorus

Table 15. Marked abnormality criteria for safety laboratory variables

Clinical laboratory variables	Units	Marked abnormality criteria	
		Low	High
Haematology			
HCT males/females	%	< 20%	> 55%
HCT males/females	%		> 60%
Hemoglobin males/females	g/L	< 60 g/L	> 180 g/L
Hemoglobin males/females	g/L		> 200 g/L
Blood chemistry			
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

Clinical laboratory variables	Units	Marked abnormality criteria Low	Marked abnormality criteria High
ALT	U/L		> 10X ULN
AST	U/L		> 10X ULN
ALT	U/L		> 20X ULN
AST	U/L		> 20X ULN
Total Bilirubin	umol/L		> 2X ULN if PreRx ≤ ULN; > 3X ULN if PreRx > ULN
Glucose, Plasma Unspecified	mmol/L	< 3 mmol/L	> 19.425 mmol/L
Na (Sodium)	mmol/L	< 130 mmol/L	> 150 mmol/L
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	
Creatinine	umol/L		≥1.5X PreRx CREAT
Creatinine	umol/L		≥ 221 umol/L
Calcium	mmol/L	< 1.871 mmol/L	≥ 0.25 mmol/L from ULN and ≥ 0.125 mmol/L from PreRx CA
Magnesium	mmol/L	< 0.5 mmol/L	> 2 mmol/L
PO4 (Phosphate)	mmol/L	Age 17-65: ≤ 0.581mmol/L	Age 17-65: ≥ 1.808 mmol/L
Magnesium		Age ≥ 66: ≤ 0.678 mmol/L	Age ≥ 66: ≥ 1.647 mmol/L
Urine			
UACR (Urinary Albumin-to-Creatinine Ratio)	mg/g		> 1800 mg/g

7.4 Appendix IV – Missing data pattern for HbA1c

Table 16. Assessment of missing data patterns by visit and treatment group (Full analysis set)

Visit	Change from Baseline in HbA1c Assessments	DAPA + MET (N = XXX)	DAPA + SAXA + MET (N = XXX)	GLIM + MET (N = XXX)
Week X	Available at Week X	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)
	No baseline assessment available	X (X.X%)	X (X.X%)	X (X.X%)
	Missed Visit	X (X.X%)	X (X.X%)	X (X.X%)
	Lost to Follow-up	X (X.X%)	X (X.X%)	X (X.X%)
	Discontinued Study Medication	X (X.X%)	X (X.X%)	X (X.X%)
	Rescued	X (X.X%)	X (X.X%)	X (X.X%)
	Cumulative Patients Excluded:			
	Primary Efficacy Analysis	X (X.X%)	X (X.X%)	X (X.X%)
	Sensitivity Analysis*	X (X.X%)	X (X.X%)	X (X.X%)
Week Y	Available at Week Y	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)
	No baseline assessment available	X (X.X%)	X (X.X%)	X (X.X%)
	Missed Visit	X (X.X%)	X (X.X%)	X (X.X%)
	Lost to Follow-up	X (X.X%)	X (X.X%)	X (X.X%)
	Discontinued Study Medication	X (X.X%)	X (X.X%)	X (X.X%)
	Rescued	X (X.X%)	X (X.X%)	X (X.X%)
	Cumulative Patients Excluded:			
	Primary Efficacy Analysis	X (X.X%)	X (X.X%)	X (X.X%)
	Sensitivity Analysis*	X (X.X%)	X (X.X%)	X (X.X%)

Missed Visit = Patient has an HbA1c at a visit before and an HbA1c at a visit after the Missed Visit.

Lost to Follow-up (e.g., Right Censored) = Patient has an HbA1c at a visit before but no HbA1c assessments after the visit.

Discontinued Study Medication = Patient has discontinued study medication prior to that visit (will result in exclusion from Primary Efficacy analysis; may or may not have an HbA1c available).

Rescued = Patient has received rescue medication prior to that visit (will result in exclusion from Primary Efficacy analysis; may or may not have an HbA1c available).

* Sensitivity analysis re-running MMRM including all values regardless of use of rescue medication or treatment discontinuation

Cumulative number (%) patients excluded from the primary efficacy analysis is the distinct patients within (LTFU + Discontinued Study Med + Rescued + No baseline available)

Cumulative number (%) patients excluded from the sensitivity analysis is the distinct patients within (LTFU + No baseline available)

7.5   Appendix V – IWQOL-Lite Scoring

The IWQOL-Lite is a 31-item self-reported assessment of quality of life in overweight or obese individuals. It scores on 5 dimensions: physical function (11 items); self-esteem (7 items); sexual life (4 items); public distress (5 items); and work (4 items). Raw scores for each scale will be computed for each of the five scales only if a minimum of 50% of the items for that scale are answered, and for the total score only if 75% of the answers for all items are completed. (The required number of minimum responses is: Physical Function=6 of 11; Self-Esteem =4 of 7; Sexual Life=2 of 4; Public Distress=3 of 5; Work=2 of 4; Total=24 of 31.) In computing raw scores, a pro-rated system for handling missing data will be used. To calculate the raw score for any scale or total score, the procedures are as follows:

1. Determine if the minimum number of items are answered for that scale. The required number of minimum responses is: Physical Function=6 of 11; Self- Esteem =4 of 7; Sexual Life=2 of 4; Public Distress=3 of 5; Work=2 of 4; Total=24 of 31.

Example 1: If an individual answered 5 of 11 Physical Function questions, the Physical Function score would be considered missing and coded as 999.

Example 2: If an individual answered 26 items on the entire scale, a valid score would be calculated for the IWQOL-Lite total.

2. Take the average of the valid items for that scale. Compute the average for the valid responses to items for that scale where 1="Never True" and 5="Always True". The average must be a number between 1 and 5. For example, if the respondent answered "3" on every item of the Physical Function scale, the mean would be 3.

Example 3: An individual answered the 11 Physical Function questions as follows (9 indicates missing question): 2, 3, 2, 4, 9, 2, 2, 3, 4, 9, 5. The individual answered 9 of 11 questions, with an average of 3.0 (27/9).

Example 4: An individual answered the 5 Public Distress questions as follows: 3, 1, 3, 4, 3. The individual answered 5 of 5 questions with an average of 2.8 (14/5).

3. Multiply that average by the total number of items for that scale. The total number of items on IWQOL-Lite scales are as follows: Physical Function=11, Self-Esteem=7, Sexual Life=4, Public Distress=5, Work=4, Total=31). Round to the nearest whole integer. For example, if the mean of the Physical Function scale is 3.0, then you would multiply 3.0 X 11 = 33.

Example 5: From the Physical Function answers in Example 3, multiply the average (3.0) times the number of total questions in the Physical Function scale (11) and round to the nearest whole integer: 3 X 11 = 33 (no need to round). This is the Physical Function Raw Score.

Example 6: From the Public Distress answers in Example 4, multiply the average (2.8) times the number of total questions in the Public Distress scale (5) and round to the nearest whole integer: 2.8 X 5 = 14 (no need to round). This is the Public Distress Raw Score.

In order to convert the IWQOL-Lite raw scores to the more familiar 0 (worst) to 100 (best) scoring using the following formulae:

1. Subtract the raw score (as calculated above) from the maximum score for each scale (Physical Function=55, Self-Esteem=35, Sexual Life=20, Public Distress=25, Work=20, Total=155).
2. Divide that difference by the range for each scale (Physical Function=44, Self-Esteem=28, Sexual Life=16, Public Distress=20, Work=16, Total=124).
3. Multiply that total by 100.

Example 7: From the Physical Function answers in Example 5, subtract the raw score (33) from the maximum score for Physical Function (55) and divide that result by the range for Physical Function (44) and multiply the result by 100: (55 - 33)/44 = .50 X 100 = 50.

Example 8: From the Public Distress answers in Example 6, subtract the raw score (14) from the maximum score for Public Distress (25) and divide that result by the range for Public Distress (20) and multiply by 100: (25 - 14)/20 = .55 X 100= 55.

An easy way to check the scoring is to enter a record with all 1's and a second record with all 5's. The first record should have all transformed scores equal to 100 and the second record should have all transformed scores equal to 0.