Clinical Study Protocol

Drug Substance	Dapagliflozin/metformin
Study Code	D1691C00007
EudraCT	[redacted]
Edition Number	1
Date	[redacted]

A Bioequivalence Study of the Fixed-dose Combination Dapagliflozin/Metformin Tablet (5 mg/850 mg) Relative to a 5-mg Dapagliflozin Tablet and an 850-mg Metformin (Glucophage® Marketed in Canada by Sanofi-Aventis) Tablet Coadministered to Healthy Volunteers in the Fasted and Fed States

Sponsor:

AstraZeneca [redacted], [redacted]

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Bioequivalence Study of the Fixed-dose Combination Dapagliflozin/Metformin Tablet (5 mg/850 mg) Relative to a 5-mg Dapagliflozin Tablet and an 850-mg Metformin (Glucophage® Marketed in Canada by Sanofi-Aventis) Tablet Coadministered to Healthy Volunteers in the Fasted and Fed States

Principal Investigator

[redacted], [redacted]

Study centre(s) and number of subjects planned

The study will be conducted at a single centre: Quintiles Drug Research Unit [redacted].

At least 36 healthy volunteers will be enrolled to ensure that 32 complete the study. A maximum of 40 healthy volunteers may be enrolled.

Study period		Phase of development
Estimated date of first subject enrolled	[redacted]	1
Estimated date of last subject completed	[redacted]	

Objectives

Primary objectives

The primary objectives of this study are:

- To demonstrate the bioequivalence of a dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet relative to 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by Sanofi-Aventis) tablets administered together in the fasted state in healthy volunteers.
- To demonstrate the bioequivalence of a dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet relative to 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by Sanofi-Aventis) tablets administered together in the fed state in healthy volunteers.

Secondary objectives

The secondary objectives of this study are:

- To describe the t_{max}, t_{last}, λ_z and $t_{1/2}$ of both dapagliflozin and metformin when administered as an immediate-release fixed-dose combination tablet and as individual tablet components in the fasted state in healthy volunteers.

- To describe the t_{max}, t_{last}, λ_z and $t_{1/2}$ of both dapagliflozin and metformin when administered as an immediate-release fixed-dose combination tablet and as individual tablet components in the fed state in healthy volunteers.

- To describe the effect of food on the pharmacokinetic profile (C_{max} , AUC, $AUC_{(0-t)}$, t_{max}, t_{last}, λ_z and elimination $t_{1/2}$ of both dapagliflozin and metformin) of the dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet compared to when administered in the fasted state in healthy volunteers.

- To assess the safety and tolerability of the dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet and of 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by Sanofi-Aventis) administered together in the fasted and fed states in healthy volunteers.

- To demonstrate bioequivalence of a dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet relative to 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by Sanofi-Aventis tablets administered together in the fasted state in healthy volunteers with analysis performed using the nominal drug dose and corrected for the measured potency of the administered formulations.

- To demonstrate bioequivalence of a dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet relative to 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by SA) tablets administered together in the fed state in healthy volunteers with analysis performed using the nominal drug dose and corrected for the measured potency of the administered formulations.

Study design

This is an open-label, randomised, 4-period, 4-treatment, 4-way crossover study conducted to determine the bioequivalence of the metformin immediate-release fixed-dose combination tablet of dapagliflozin/metformin (5 mg/850 mg) relative to single tablets of dapagliflozin (5 mg) and metformin (850 mg) Glucophage® (marketed in Canada by Sanofi-Aventis) administered together in healthy volunteers under fasting and fed conditions. At least 36 healthy volunteers will be enrolled and randomized to 1 of 4 treatment sequences according to a William's design for a 4-period, 4-treatment, 4-way crossover study. Treatments A and B are to be administered in the morning in a fasted state, while Treatments C and D are to be administered in the morning within approximately 30 minutes of starting a standard high-fat/high-calorie breakfast (fed state). There will be at least 5 minutes between

completion of the breakfast and dosing. Serial blood samples for pharmacokinetics analysis of dapagliflozin and metformin will be collected over a 72-hour interval following dosing in treatment periods 1, 2, 3, and 4 (Visits 2 to 5). The washout between each dose will be at least 7 days but no longer than 14 (or 21) days.

Target subject population

The target population is healthy male and female volunteers aged 18 to 55 years with a body mass index of between 18 and 30 kg/m^2 (inclusive). Healthy volunteers should be within 15% of their ideal body weight (per Ciba-Geigy or Metropolitan Life tables).

Investigational medicinal product, dosage and mode of administration

Treatment A: Single oral doses of 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by Sanofi-Aventis) tablets administered together in the fasted state.

Treatment B: A single oral dose of dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet in the fasted state.

Treatment C: Single oral doses of 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by Sanofi-Aventis) tablets administered together in the fed state.

Treatment D: A single oral dose of dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet in the fed state.

Comparator, dosage and mode of administration

None.

Duration of treatment

The total study duration for each healthy volunteer will be approximately 9 weeks. The time from screening and enrolment (Visit 1) to randomisation (Day 1, Visit 2) will be a maximum of 28 days. There will be 4 treatment periods (Visit 2 to Visit 5), each of 5 days (Day -1 until Day 4). A single oral dose of the dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet or single oral doses of each individual tablet will be administered under fasting or fed conditions on Day 1 of each treatment period. The washout between each dose will be at least 7 days but no longer than 14 (or 21) days. A follow-up visit (Visit 6) will take place 7 to 10 days post last dose.

Outcome variable(s):

- Pharmacokinetics
  - Primary: C_{max}, AUC and $AUC_{(0-t)}$ for each of dapagliflozin and metformin when administered as an immediate-release fixed-dose combination tablet and as individual tablets in the fasted and fed state, respectively

  - Secondary: t_{max}, t_{last}, λ_z, $t_{1/2}$ of dapagliflozin and metformin when administered as an immediate-release fixed-dose combination tablet and as individual tablets in the fasted and fed state, respectively

- Safety

  - Vital signs (blood pressure and pulse), electrocardiogram, clinical laboratory safety data (clinical chemistry, haematology and urinalysis), physical examination and adverse events

Statistical methods

The analysis will be performed using the nominal drug dose and corrected for the measured potency of the administered formulations. Point estimates and 90% confidence intervals for C_{max}, $AUC_{(0-t)}$, and AUC will be calculated for the Test to Reference ratios of geometric means of dapagliflozin and metformin using a linear mixed effect model. The reference and test treatments are defined as Treatments A and B, respectively, for comparisons within the fasted state, and as Treatments C and D, respectively, for comparisons within the fed state. These estimates will be constructed from the results of fitting the linear mixed effect models for log-transformed data with treatment sequence and period as fixed effects and subject within sequence as a random effect. Point estimates of the ratios and their confidence intervals will then be transformed back to original scale in order to give point estimates for the ratios of geometric means and their confidence intervals. As per guidelines from Health Canada, bioequivalence will be demonstrated if the 90% confidence interval of the ratio of geometric means of AUC and C_{max} of the test to reference is within 80% to 125%.

Effect of food for the dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet will be analysed with a similar model as described above.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol (CSP).

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APT	Activated partial thromboplastin
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from time zero extrapolated to infinity
$\%AUC_{ex}$	Percentage of the area under the plasma concentration-time curve obtained by extrapolation
%AUC(0-t)/AUC	Percent of the area measured by AUC(0-t) relative to the extrapolated total AUC
$AUC_{(0-t)}$	Area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration
$AUC_{(0-inf)}$	Area under the concentration time-curves from time zero to infinity
BMI	Body mass index
BMS	Bristol-Myers Squibb
$\%C_0/C_{max}$	Percent of predose concentration relative to C_{max}
C_{last}	Last observed quantifiable analyte concentration.
C_{max}	Observed maximum analyte concentration
CPA	Clinical Pharmacology Alliance
CRF	Case report form (electronic/paper)
CSA	Clinical study agreement
CSP	Clinical study protocol
CSR	Clinical study report
CV	Coefficient of variation
CV%	Coefficient of variation in %
ECG	Electrocardiogram

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IR	Immediate release
LLOQ	Lower limit of quantification
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
Min	Minimum
OAE	Other significant adverse event (see definition in Section 11.2.1)
OTC	Over-the-counter
PI	Principal Investigator
PK	Pharmacokinetic(s)
QTcF	QC interval corrected for heart rate using Fridericia's formula
Rsq	Regression coefficient
SA	Sanofi-Aventis
SAE	Serious adverse event (see definition in Section 6.4.2).
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter 2
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation or special term	Explanation
$t_{1/2}$	Terminal half-life
T2DM	Type 2 diabetes mellitus
t_{last}	Time of last quantifiable analyte concentration
t_{max}	Time to reach maximum analyte concentration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UTI	Urinary tract infection
λ_z	Terminal rate constant

1. INTRODUCTION

1.1 Background

Type 2 diabetes mellitus (T2DM) is a progressive disease characterised by worsening glycemic control over the years. While dietary and lifestyle interventions remain the fundamental approach to the treatment of T2DM, a large number of patients require daily administration of pharmacologic agents to achieve adequate glycemic control. Despite the fact that there are many medications approved for treatment of T2DM, achieving and maintaining treatment goals can be challenging, and new treatment options are required.

Dapagliflozin is a member of a new class of antihyperglycaemic therapeutic agents for treatment of T2DM and has been developed as an orally active drug. Dapagliflozin is a stable, competitive, reversible, highly selective inhibitor of the human renal sodium-glucose cotransporter (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose and thereby promoting its urinary excretion. Such an approach to antidiabetic therapy provides an opportunity for achieving significant glycaemic efficacy with a relatively low risk of hypoglycaemia, and since the mechanism of action is independent of insulin secretion or insulin action, it is potentially applicable to a broad spectrum of patients, including those currently treated with metformin, that do not have optimal glycemic control. For further information about dapagliflozin, refer to the Investigator's Brochure (IB).

Metformin hydrochloride is considered the first-line drug for treatment of hyperglycaemia caused by T2DM. Metformin decreases elevated blood glucose with predominant effects on fasting hyperglycaemia by reducing hepatic glucose output and also by reducing insulin resistance. The immediate release (IR) forms are widely approved for the treatment of T2DM. Available second-line drugs, used alone or in combination with metformin where treatment targets cannot be maintained on metformin alone, are associated with a number of undesirable side effects that can necessitate a change in medication or exacerbate comorbidities associated with diabetes. For further information about metformin, refer to the Summary of Product Characteristics found in the Investigational Medicinal Product Dossier.

Given the complementary effects of dapagliflozin and metformin on glycaemic control, a fixed-dose combination (FDC) product containing dapagliflozin and metformin has been developed.

This study will be conducted in order to determine the bioequivalence of a metformin IR FDC tablet of dapagliflozin and metformin (dapagliflozin/metformin [5 mg/850 mg]) versus a 5-mg dapagliflozin tablet and an 850-mg metformin tablet (Glucophage® marketed in Canada by Sanofi-Aventis [SA]) under fasting and fed conditions in healthy volunteers.

1.2 Research hypotheses

The research hypotheses to be tested are:

- The IR FDC dapagliflozin/metformin (5 mg/850 mg) tablets are bioequivalent to the individual tablets when coadministered as demonstrated by C_{max}, AUC and $AUC_{(0-t)}$ for each of dapagliflozin and metformin, respectively, when administered in the fasted state.

- The IR FDC dapagliflozin/metformin (5 mg/850 mg) tablets are bioequivalent to the individual tablets when coadministered as demonstrated by C_{max}, AUC and $AUC_{(0-t)}$ for each of dapagliflozin and metformin, respectively when administered in the fed state.

1.3 Rationale for conducting this study

In a previous study, the metformin IR FDC tablet of dapagliflozin and metformin was compared to the administration of the individual tablets of dapagliflozin and metformin. This was a 2-part, open-label, randomized, single-centre, Phase 1 bioequivalence study comparing (Part I) the FDC dapagliflozin/metformin IR tablet (2.5 mg/850 mg) versus the free combination of the dapagliflozin tablet (2.5 mg) and metformin IR tablet (850 mg); and (Part II) comparing the FDC dapagliflozin/metformin IR tablet (5 mg/1000 mg) versus the free combination of the dapagliflozin tablet (5 mg) and metformin IR tablet (1000 mg) in healthy volunteers, both parts in the fed state. The purpose of the study was to compare the bioequivalence of the FDCs of 2.5 mg/850 mg and 5 mg/1000 mg to the administration of the individual products of dapagliflozin and metformin. The chosen doses were the highest and lowest of the 4 fixed-dose, IR combinations planned to be marketed (2.5/850; 5/850; 2.5/1000; and 5/1000). The study comprised 2 separate groups of 60 healthy volunteers who received single doses of the combination or individual components in a randomized open-label manner within 30 minutes of a non-high fat breakfast. The primary endpoint was the ratio of the C_{max}, $AUC_{(0-t)}$ and AUC_{inf}. The standard criteria to consider 2 formulations bioequivalent is that the 90% confidence of the ratio of the primary endpoints should fall between 0.80 and 1.25 for both dapagliflozin and metformin. The FDCs of both tablets were generally well tolerated. The most common adverse events (AEs) were headache and gastrointestinal intolerance. The other safety issue of note was that one female volunteer had an episode of clinical pyelonephritis that started 3 days after the second dose and responded to antibiotic treatment.

The individual tablets of metformin hydrochloride (Glucophage®) were manufactured by Merck. The IR metformin tablet to be used in the present study is manufactured by Merck and marketed by SA. Health Canada requires that bioequivalence be demonstrated to the marketed product in single dose cross-over comparative bioavailability studies, so this study is being conducted in order to meet this requirement. The criteria for demonstrating bioequivalence as per the guidelines are that the 90% confidence interval of the relative mean AUC of the test to reference product should be within 80% to 125%, and the relative mean measured C_{max} of the test to reference product should be between 80% and 125%. There are 4 different FDC tablets: 2.5 mg/850 mg; 2.5 mg/1000 mg; 5 mg/850 mg; and 5 mg/1000 mg of dapagliflozin/metformin, respectively. The tablet to be utilised in this study is the dapagliflozin/metformin 5 mg/850 mg IR FDC tablet. Normally bioequivalence studies are performed with the highest dose, as the bioequivalence issues are most likely to be demonstrated with the highest dose in compounds with linear pharmacokinetics (PK), hence

the choice of the 5-mg dose for dapagliflozin. Metformin, however, has dose-related absorption with diminished absorption with higher doses. Therefore, the lower dose is more sensitive to the performance of the formulation, so the 850-mg dose of metformin is to be studied. For further details on the rationale for dose selection, refer to Section 3.2.

1.4 Benefit/risk and ethical assessment

Dapagliflozin's novel mechanism of action, inhibition of SGLT2, can result in lowering of plasma glucose regardless of the patient's insulin sensitivity and β-cell functional secretory status. As the mechanism is independent of insulin secretion or insulin action, this approach to antidiabetic therapy provides an opportunity to achieve clinically important glycemic efficacy with a relatively low risk of hypoglycaemia. Furthermore, the insulin independent mechanism of action of SGLT2 inhibitors suggests that this treatment is applicable to a broad spectrum of patients and every stage of T2DM. The increased excretion of glucose may promote weight loss or prevent weight gain, a potential benefit for many patients with diabetes. Dapagliflozin (Forxiga) is approved for marketing access in the European Union and Australia.

The inhibition of SGLT2 results in increased urinary glucose concentrations, which may lead to an identified increased risk of developing urinary tract infections (UTIs) and mycotic infections. Neither UTIs nor mycotic infections were reported in clinical Phase 1 studies; however, in clinical Phase 3 studies, patients receiving dapagliflozin 10 mg showed an increased frequency of UTIs (4.3%) and genital infections (4.8%) compared to patients receiving placebo (UTI, 3.7%; and genital infections, 0.9%; for details, refer to the IB). Events of UTI or mycotic infections were generally successfully treated with antimicrobial agents and rarely led to discontinuation.

Based on the osmotic diuretic effect of dapagliflozin and results of animal and clinical studies, there may be a potential risk for this compound to cause hypovolemia or electrolyte imbalance. However, as hypovolemia has not been observed in studies where single doses of dapagliflozin have been administered, the risk for hypovolemia in this study is considered very low.

Neither dapagliflozin nor metformin showed any changes in their PK profile when administered together compared to when administered alone (refer to the IB). The clinical program shows no imbalances of hepatic enzyme elevations in Phase 3 studies. Where observed, enzyme elevations have not shown any specific pattern with regards to time of exposure and were generally reversible. One subject receiving dapagliflozin experienced a liver AE with diagnoses of drug-induced hepatitis and/or autoimmune hepatitis. Even though dapagliflozin and metformin have a low propensity for hypoglycaemia, 20% glucose solution or orange juice will be available during periods of admission as a safety precaution and will be given if a healthy volunteer develops any symptoms of hypoglycaemia. In addition, intravenous glucose may be given if considered necessary by the Investigator. AstraZeneca will immediately notify the Principal Investigator (PI) of important safety data (eg, toxicology, absorption, distribution, metabolism and excretion, or teratology) that become available during the study.

2. STUDY OBJECTIVES

2.1 Primary objectives

The primary objectives of this study are:

- To demonstrate the bioequivalence of a dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet relative to 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by SA) tablets administered together in the fasted state in healthy volunteers

- To demonstrate the bioequivalence of a dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet relative to 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by SA) tablets administered together in the fed state in healthy volunteers

2.2 Secondary objectives

The secondary objectives of this study are:

- To describe the time to reach maximum analyte concentration (t_{max}), time of last quantifiable analyte concentration (t_{last}), terminal rate constant(λ_z), and terminal half-life ($t_{1/2)}$ of both dapagliflozin and metformin when administered as an IR FDC tablet and as individual tablet components in the fasted state in healthy volunteers.

- To describe the t_{max}, t_{last},λ_z and $t_{1/2}$ of both dapagliflozin and metformin when administered as an IR FDC tablet and as individual tablet components in the fed state in healthy volunteers.

- To describe the effect of food on the PK profile (C_{max}, AUC, $AUC_{(0-t)}$, t_{max}, t_{last}, λ_z and elimination $t_{1/2}$ of both dapagliflozin and metformin) of the dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet compared to when administered in the fasted state in healthy volunteers.

- To assess the safety and tolerability of the dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet and of 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by SA) administered together in the fasted and fed states in healthy volunteers.

- To demonstrate bioequivalence of a dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet relative to 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by SA) tablets administered together in the fasted state in healthy volunteers with analysis performed using the nominal drug dose and corrected for the measured potency of the administered formulations.

- To demonstrate potency-corrected bioequivalence of a dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet relative to 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by SA) tablets administered together in the fed

state in healthy volunteers with analysis performed using the nominal drug dose and corrected for the measured potency of the administered formulations.

3. STUDY PLAN AND PROCEDURES

This CSP has been subject to a peer review according to AstraZeneca standard procedures.

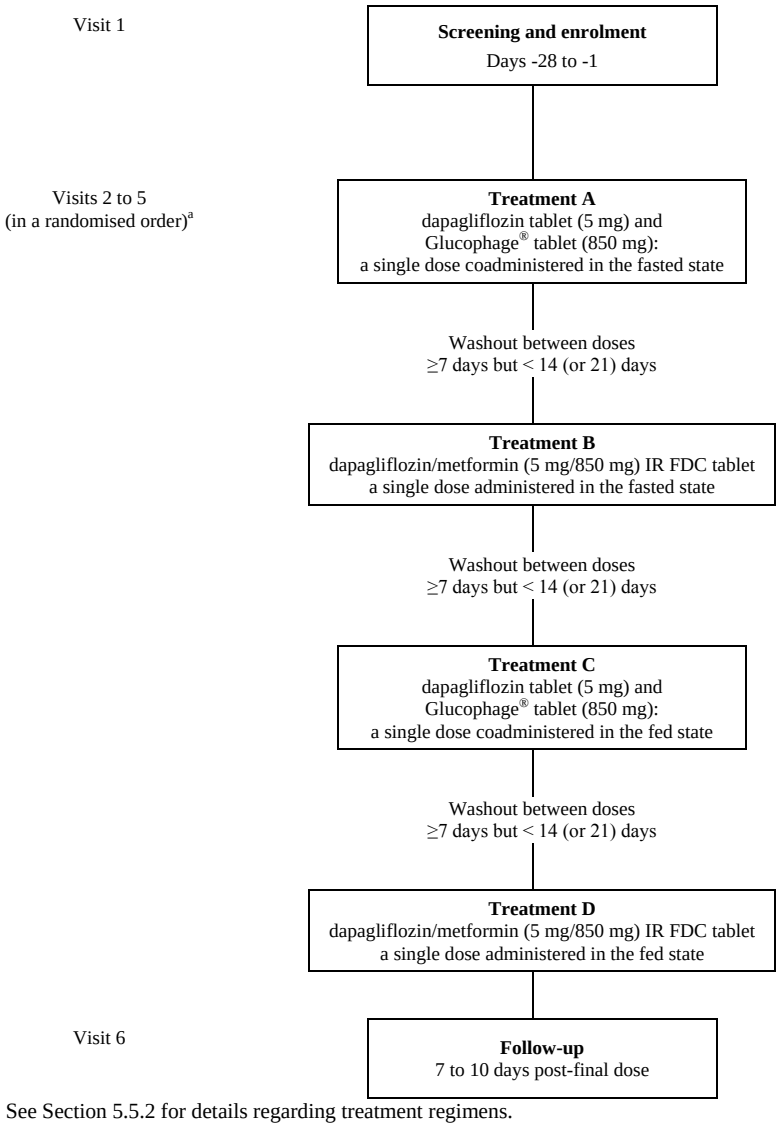
3.1 Overall study design and flow chart

This is an open-label, randomised, 4-period, 4-treatment, 4-way crossover study conducted to determine the bioequivalence of the dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet relative to single tablets of dapagliflozin (5 mg) and metformin (850 mg) Glucophage® (marketed in Canada by SA) administered together in healthy volunteers under fasting and fed conditions.

Thirty-six healthy volunteers will be enrolled initially in order to have 32 completed and evaluable volunteers. Up to 40 healthy volunteers may be enrolled. Volunteers will be randomised to 1 of 4 treatment sequences according to a William's design for a 4-period, 4-treatment, 4-way crossover study. Treatments A and B are to be administered in the morning in a fasted state, while Treatments C and D are to be administered in the morning after completing a standard high fat/high calorie breakfast (fed state). Doses will be administered within approximately 30 minutes of starting the breakfast. There will be at least 5 minutes between completion of the breakfast and dosing.

The total study duration for each healthy volunteer will be approximately 9 weeks. The time from screening and enrolment (Visit 1) to randomisation (Day 1, Visit 2) will be a maximum of 28 days. There will be 4 treatment periods (Visit 2 to Visit 5), each of 5 days (Day -1 until Day 4, 72 hours postdose). A single oral dose of the dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet or single oral doses of each individual tablet will be administered under fasting or fed conditions on Day 1 of each treatment period, see Figure 1. Serial blood samples for PK analysis of dapagliflozin and metformin will be collected over a 72-hour interval following dosing in treatment periods 1, 2, 3, and 4 (Visits 2 to 5), see Figure 1. The washout between each dose will be at least 7 days but no longer than 14 (or 21) days. In each treatment period, subjects will be admitted to the clinical facility on Day -1. Volunteers will be discharged from the facility on Day 4 of each treatment period after the PK sampling and all safety evaluations have been completed. A follow-up visit (Visit 6) will take place 7 to 10 days post last dose.

Figure 1 Study flow chart



[a] See Section 5.5.2 for details regarding treatment regimens.

Table 1 Study plan

Visit	**1**	**2 to 5**	**6**
Visit description	**Screening**	**Treatment periods 1 to 4**	**Follow-up**
Visit window	**≤28 days prior to randomisation**	**Day -1 to Day 4**	**7 to 10 days after last dose**
Signed Informed Consent	X		
Inclusion/exclusion criteria	X	X[a]	
Concomitant medication	X	X	X
Medical /surgical history	X		
Physical examination	X	X[b]	X
Serology[c]	X		
Demographics	X		
Weight and height	X		
Urine drugs of abuse screen and alcohol breath test[d]	X	X	
12-lead ECG	X		X
Vital signs (blood pressure, heart rate)	X	X[e]	X
Clinical chemistry, haematology, urinalysis	X	X[f]	X
Coagulation	X		
Randomisation		X[g]	
PK blood sampling[h]		X	
Administration of investigational medicinal product (IMP)		X[i]	
Pregnancy test (urine)[j]	X	X[k]	X
Serum follicle stimulating hormone (FSH)[l]	X		
Adverse events		X[m]	X
Serious adverse events	X	X	X

ECG=electrocardiogram; PK=pharmacokinetics; IMP=investigational medicinal product; FSH=follicle stimulating hormone; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] Eligibility will be confirmed prior to each dosing.
[b] Brief physical examination on Day -1 at Visits 2 to 5.
[c] Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) screening.
[d] Drugs of abuse and alcohol test at screening and each admission to the clinical unit.
[e] Once daily during the residential period, ie, Day -1 and Day 1 (predose) to Day 4.
[f] On Day -1 at Visits 2 to 5.

[g] Predose Day 1 of treatment period 1 (Visit 2).
[h] Pharmacokinetic blood samples will be collected at 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 42, 48, 54, 60 and 72 hours postdose.
[i] Day 1 of each treatment period (Visits 2 to 5).
[j] Female volunteers must have a confirmed negative urine pregnancy test at screening and on Day -1 of each treatment period (Visits 2 to 5) prior to dosing.
[k] Day -1 of each treatment period (Visits 2 to 5).
[l] Postmenopausal females only. The FSH levels must be in the laboratory-defined postmenopausal range.
[m] From first dose in treatment period 1 (Visit 2).

3.2 Rationale for study design, doses and control groups

An open-label, randomised, 4-period crossover design will be used to assess the bioequivalence of a metformin IR FDC dapagliflozin/metformin (5 mg/850 mg) tablet relative to individual tablets administered together in both the fed and fasted states in healthy volunteers.

Four different IR FDC dapagliflozin/metformin tablets have been developed: 2.5 mg/850 mg; 5 mg/850 m; 2.5 mg/1000 mg; and 5 mg/1000 mg. In this study, the IR FDC that will be most sensitive in demonstrating issues with bioequivalence when compared to the administration of the individual components will be used, ie, the 5 mg/850 mg tablet. The lowest dose of metformin (850 mg) in the IR FDC has been chosen as the bioavailability of metformin is nonlinear (as described in the Bristol-Myers Squibb [BMS] metformin package insert). This characteristic of metformin means that the lower dose of metformin is more sensitive to demonstrating issues with bioavailability compared to the higher dose as there is naturally a greater limit on the bioavailability of the higher dose of metformin compared to the lower dose. Thus with a higher dose of metformin, issues of bioavailability may be masked by the diminished bioavailability of the higher dose. The highest dose of dapagliflozin (5 mg) has been chosen as the PK of dapagliflozin is linear. Therefore, if there is an issue with the bioavailability of dapagliflozin it will be most evident with a higher dose than with a lower dose, so the highest dose of dapagliflozin in the IR FDC tablet will be studied.

The sample size of 36 (32 evaluable) healthy volunteers is based on the desire to obtain adequate PK and safety data to achieve the objectives of the study while exposing as few volunteers as possible to study medication and procedures. Exposure to study drug in this study is limited to 4 single doses for each volunteer.

A washout of at least 7 days (but no longer than 14 [or 21] days) will separate each treatment period in order to reduce the risk for carry-over effects.

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record (the subject screening log) of volunteers who entered prestudy screening.

Each volunteer should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study, healthy volunteers should fulfil the following criteria:

1. Provision of signed and dated informed consent prior to any study-specific procedures

2. Healthy volunteers aged 18 to 55 years inclusive with suitable veins for cannulation or repeated vein puncture

3. Male volunteers should be willing to use barrier contraception, ie, condoms and spermicide, from the day of dosing until at least 3 months after dosing with the investigational medicinal product (IMP).

4. Nonpregnant, nonlactating female volunteers who if premenopausal are using adequate birth control, eg, oral, injectable, transdermal or implanted hormonal contraceptives, vaginal contraceptive ring, intrauterine device/intrauterine system, tubal ligation, vasectomised sexual partner (with confirmed negative sperm counts) or true sexual abstinence. Postmenopausal females should have FSH levels in the laboratory defined postmenopausal range. All females must have a negative pregnancy test within 24 hours prior to dosing with IMP.

5. Volunteers should have a body mass index (BMI) between 18 and 30 kg/m^2 inclusive (ie, within 15% of normal range) and weigh at least 50 kg and no more than 100 kg. Volunteers should be within 15% of their ideal body weight (as per Ciba-Geigy or Metropolitan Life tables).

4.2 Exclusion criteria

Healthy volunteers should not enter the study if any of the following exclusion criteria are fulfilled:

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in the study.

2. History or presence of gastrointestinal, hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.

3. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of IMP.

4. Any clinically significant abnormalities in clinical chemistry, haematology, or urinalysis results as judged by the Investigator.

5. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody and human immunodeficiency virus (HIV).

6. Any clinically abnormal vital signs, after 10 minutes sitting or supine rest, as judged by the Investigator.

7. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG that may interfere with individual safety evaluation.

8. Prolonged QC interval corrected for heart rate using Fridericia's formula (QTcF) >450 ms or shortened QTcF <350 ms or family history of long QT syndrome.

9. Known or suspected history of drug abuse as judged by the Investigator.

10. Current smokers who smoke more than 5 cigarettes per day (or equivalent use of tobacco products) or cannot give up smoking during the study.

11. History of alcohol abuse or volunteers who consume more than 14 (female volunteers) or 21 (male volunteers) units of alcohol a week (unit = 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer).

12. Positive screen for drugs of abuse or alcohol at screening or at any of the admissions to the clinical unit.

13. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator or history of hypersensitivity to drugs with a similar chemical structure or class to dapagliflozin or metformin

14. Excessive intake of caffeine containing drinks eg, coffee, tea, caffeine-containing energy drinks, and cola (more than 5 cups of coffee or equivalent per day)

15. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP

16. Use of any prescribed or nonprescribed medication including antacids, analgesics other than paracetamol/acetaminophen, herbal remedies, vitamins and minerals during the two weeks prior to the first administration of the IMP or longer if the medication has a long half-life. Occasional use of paracetamol/acetaminophen and adrenergic nasal spray is allowed. Hormone replacement therapy and oral contraceptives are allowed for females.

17. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade or other products containing grapefruit or Seville oranges within 7 days before the first administration of the IMP

18. Plasma donation within one month of screening or any blood donation/blood loss >500 mL during the 3 months prior to screening

19. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 3 months of the first administration of investigational medicinal product in this study. The period of exclusion begins at the time of the last dose in the prior study. Note: Healthy volunteers consented and screened but not dosed in this study or a previous Phase 1 study, are not excluded.

20. Previous randomisation to treatment in the present study

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

22. Previous participation in an AstraZeneca or BMS dapagliflozin study.

23. Judgment by the Investigator that the healthy volunteer should not participate in the study if they are considered unlikely to comply with study procedures, restrictions and requirements.

For procedures for withdrawal of incorrectly enrolled volunteers, see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

1. Fasted treatment: Fast from at least 10 hours before planned start of dosing. A moderate amount of water is allowed up to 2 hours prior to dosing and may be resumed 2 hours after dosing. A standardised meal can be given 4 hours after dosing.

   Fed treatment: Fast from at least 10 hours before the standard high-fat, high-calorie breakfast. Dosing will occur 30 minutes after the start of the high-fat, high-calorie breakfast. There will be at least 5 minutes between completion of the breakfast and dosing. Water is allowed for up to 1 hour prior to dosing and again 1 hour after dosing. A standardised meal can be given 4 hours after dosing.

2. Eat and drink only the standardised meals and drinks provided (apart from water) during the residential period in the unit.

3. Abstain from consuming any of the following:

   – Alcohol from 72 hours before admission, during the residential period and for 72 hours before the study follow-up visit.

   – Energy drinks containing taurine or glucuronolactone, eg, Red Bull from 72 hours before admission, during the residential period and for 72 hours before the study follow-up visit.

   – Caffeine-containing drinks during the residential period. Excessive intake of caffeine should be avoided between discharge from the unit and the study follow-up visit.

   – Poppy seeds found in speciality bread from time of consent until after the final medical examination at the study follow-up.

– Grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade or other products containing grapefruit or Seville oranges from 7 days before first administration of IMP until after the final medical examination at the study follow-up.

4. Abstain from nicotine use, smoking and drugs of abuse from time of consent until after the final medical examination at the study follow-up.

5. Abstain from taking any medication (prescribed or over-the-counter (OTC) products), other than hormone replacement therapy (females), oral contraceptives (females), paracetamol/acetaminophen and adrenergic nasal spray in recommended doses from 2 weeks (3 weeks for drugs with enzyme-inducing properties such as St. John's Wort) prior to the first administration of investigational medicinal product until after the final medical examination at the study follow-up. However, this should not obviate necessary medical treatment. If any medication is necessary during the residential period, it should be prescribed by the Investigator and the AstraZeneca Clinical Pharmacology Alliance (CPA) physician should be informed (Section 13.1).

6. Refrain from strenuous physical activity, which is not within the volunteer's normal daily routine, from 7 days prior to admission to the unit until after the final medical examination at the study follow-up.

7. Abstain from blood or plasma donation until 3 months after the final medical examination at the study follow-up.

5.2 Subject enrolment and randomisation

The PI or delegate will:

1. Obtain signed informed consent from the potential volunteer before any study-specific procedures are performed.

2. Assign potential volunteer a unique 7-digit enrolment number, beginning with '[redacted]'

3. Determine volunteer eligibility. See Sections 4.1 and 4.2.

4. Assign eligible volunteer a unique randomisation code (subject number), beginning with eg '[redacted].'

Volunteers will be randomised to 1 of 4 treatment sequences according to a William's Design for 4-period, 4-treatment, 4-way crossover study.

If a volunteer withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

5.2.1 Procedures for randomisation

Randomisation codes will be assigned strictly sequentially as volunteers become eligible for randomisation.

A randomisation list, with randomisation codes and treatments will be produced by Quintiles using the global randomisation GRand program.

5.3 Procedures for handling subjects incorrectly enrolled or randomised

Volunteers who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

When a volunteer does not meet the selection criteria, is randomised in error, and this is identified before dosing, the volunteer should be withdrawn from the study. A discussion should occur between the AstraZeneca CPA physician and the Investigator regarding whether a replacement should be considered. The CPA physician is to ensure all such decisions are appropriately documented.

If a volunteer who does not meet the selection criteria has been dosed before the error is identified, the volunteer should be advised to continue assessments to ensure their safety, and the AstraZeneca CPA physician should be informed of the error. The volunteer should be withdrawn from the study prior to further dosing.

5.4 Blinding and procedures for unblinding the study

This is an open-label study.

5.5 Treatments

5.5.1 Identity of investigational medicinal product(s)

Investigational medicinal product(s)	Dosage form and strength	Manufacturer
Dapagliflozin	5-mg film-coated tablet IR for oral administration	Bristol-Myers Squibb
Dapagliflozin/metformin	5-mg/850 mg film-coated IR tablet for oral administration	AstraZeneca
Metformin Glucophage®	850-mg IR tablet for oral administration	Merck

All IMPs will be packaged and labelled in accordance with Good Manufacturing Practice (GMP) and Annex 13. The IMPs will be supplied in bulk to Quintiles by AstraZeneca.

5.5.2 Doses and treatment regimens

The following treatments will be administered to each healthy volunteer in 1 of 4 sequences:

Treatment A: Single oral doses of 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by SA) tablets administered together in the fasted state.

Treatment B: A single oral dose of the dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet in the fasted state.

Treatment C: Single oral doses of 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by SA) tablets administered together in the fed state.

Treatment D: A single oral dose of the dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet in the fed state.

The tablets must be swallowed whole and must not be chewed or crushed.

For the fasted state, the volunteers should fast at least 10 hours before dosing. The IMPs will be administered with 240 mL of water and the volunteers should remain fasting until 4 hours after dosing. Water will be allowed as desired up to 2 hours before and from 2 hours after dosing. Thereafter, the standard diets should be administered.

For the fed state, the volunteers, should fast at least 10 hours before the standard high-fat, high-calorie breakfast. Volunteers will start a high-fat, high-calorie breakfast approximately 30 minutes prior to dosing. There will be at least 5 minutes between completion of the breakfast and dosing. After breakfast, the volunteers should remain fasting for the following 4 hours. Water will be allowed as desired up to 1 hour before breakfast and 1 hour after dosing. Thereafter, the standard diets should be administered.

The high-fat, high-calorie breakfast should consist of between 800 and 1000 calories and should derive approximately 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat. The composition of the meal will be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content [%]). The high-fat, high-calorie breakfast will follow the recommendations provided in the European Medicines Agency Guideline on the Investigation of Bioequivalence 2010 as well as the Food and Drug Administration (FDA) Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence studies 2002. An example of a high-fat, high-calorie breakfast consists of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes (115 g) and 240 mL of whole milk.

5.5.3 Additional study drug

Not applicable.

5.5.4 Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling.

The label will include the following information:

- Name of sponsor (AstraZeneca)
- Study drug(s) dosage form, route of administration, and quantity of dosage units
- Study code
- Order number (to identify the contents and packaging operation)
- Directions for use (for oral use)
- The period of use, eg, expiry date
- Storage conditions
- "For clinical trial use only"

5.5.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IMP label on the container specifies the appropriate storage.

The dispensing and retention of reserve samples of IMP will be performed with the FDA Code of Federal Regulations 21, Part 320 Bioavailability and Bioequivalence requirements.

5.6 Concomitant and post-study treatment(s)

Apart from occasional use of paracetamol/acetaminophen and OTC adrenergic nasal spray in recommended doses, hormone replacement therapy (females), oral contraceptives (females), no concomitant medication or therapy, prescribed or nonprescribed, will be allowed from 2 weeks (3 weeks for drugs with enzyme-inducing properties such as St John's Wort) prior to the first administration of IMP until after the final medical examination at the follow-up visit. Healthy volunteers should be instructed that no other medication is allowed including herbal remedies and OTC products without the consent of the Investigator.

Other medication that is considered necessary for the volunteer's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form (CRF).

5.7 Treatment compliance

The administration of all study drugs (including IMPs) should be recorded in the appropriate sections of the CRF.

Treatment compliance will be assured by supervised administration of the IMP by the Investigator or delegate.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the healthy volunteer.

At the end of the study, study site personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Destruction must not take place unless AstraZeneca has approved it. Certificates of delivery and destruction must be signed.

5.8 Discontinuation of investigational medicinal product

Healthy volunteers may be discontinued from IMP in the following situations:

- Volunteer decision. The volunteer is free at any time to discontinue treatment, without prejudice to further treatment.
- Adverse event
- Severe noncompliance to study protocol
- Randomisation in error

5.8.1 Procedures for discontinuation of a subject from investigational medicinal product

A healthy volunteer that decides to discontinue IMP will always be asked about the reason(s) and the presence of any AEs. If possible, he/she will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4).

If a healthy volunteer is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Healthy volunteers are free at any time to withdraw from study (IMP and assessments), without prejudice to further treatment (withdrawal of consent). Such volunteers will always be asked about the reason(s) and the presence of any AE. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.4.3 and 6.4.4). Healthy volunteers who are withdrawn from the study by the Investigator due to AEs after dosing will not be replaced. Healthy volunteers who withdraw for any other reason before dosing or for reasons other than AEs after dosing may be replaced.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below and the timing of assessments are detailed in the Study Plan (Table 1).

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to, or after, but as close as possible to the scheduled time point. The priority order (in terms of precision of time) at a particular time point will be:

1. Blood samples for PK

2. Vital signs

3. Clinical laboratory assessments (clinical chemistry, haematology, urinalysis)

Predose assessments (except the predose PK sampling) may be performed up to 60 minutes prior to dose. Predose PK samples should be taken within 1 hour of dose. Acceptable deviations from scheduled assessment times of PK samples from 0.25 hours up to and including 1 hour will be ±5 minutes. For PK samples to be taken from 1.5 hours up to and including 72 hours, acceptable time deviations from scheduled assessment times will be ±10 minutes.

6.1 Recording of data

The Investigator will ensure that data are recorded on the paper CRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed paper CRFs. A copy of the completed paper CRFs will be archived at the study site.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

At enrolment (Visit 1), each healthy volunteer will provide written and signed informed consent prior to starting any study specific procedures.

Demographic data and other baseline characteristics will be recorded and will include: date of birth, gender, and race, habits of alcohol and caffeine consumption, and smoking history.

Eligibility will be confirmed through the following procedures:

- A standard medical, medication, and surgical history with review of the inclusion and exclusion criteria with the volunteer
- A complete physical examination
- Height, weight, and calculation of BMI
- Vital signs (resting supine blood pressure and pulse)

- Recording a resting 12-lead paper ECG
- Blood samples for routine clinical chemistry and haematology analyses and screen for HBsAg, antibodies to HCV and antibodies to HIV. Postmenopausal women will undergo a serum FSH level test.
- A urine sample for routine urinalysis, drugs of abuse screen and pregnancy test (females only).
- Breath test for alcohol.
- Serious adverse event (SAE) and concomitant medications questioning

6.2.2 Follow-up procedures

A poststudy medical examination will be performed 7 to 10 days after the last dose. This will be similar to the one performed at screening and will include a complete physical examination, vital signs, recording of a 12-lead paper electrocardiogram (ECG), blood samples for clinical chemistry and haematology analyses, a urine sample for urinalysis, and AE and concomitant medication questioning.

6.3 Efficacy

Not applicable.

6.4 Safety

The PI is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, clinical laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and nonserious AEs.

6.4.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, or follow-up), that fulfils one or more of the following criteria:

- Results in death

- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the healthy volunteer or may require medical intervention to prevent one of the outcomes listed above.

Any event of cancer, drug dependency/abuse, clinical laboratory abnormalities fulfilling the Hy's law definition alanine aminotransferase (ALT)/aspartate aminotransferase (AST) greater than 3 times ULN; and total bilirubin greater than 2 times ULN; or overdose (defined as the accidental or intentional ingestion of any dose of the investigational medicinal product that is considered both excessive and medically important) should be reported as an SAE using the most relevant SAE criteria, as judged by the Investigator.

For further guidance on the definition of an SAE, see Appendix B to the CSP.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from administration of the first dose of IMP throughout the treatment periods and including the follow-up visit (Visit 6).

Serious adverse events will be recorded from the time of informed consent up to and including the follow-up visit.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the healthy volunteer's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any healthy volunteer with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE:

- Adverse event (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not

- Investigator causality rating against the IMP (yes or no)
- AE caused healthy volunteer's withdrawal from study *(*yes or no*)*
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Adverse event is serious due to:
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE

The following intensity ratings will be used:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)
- Very severe (debilitating, significantly incapacitates patient despite symptomatic therapy)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. However, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

The Investigator will assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational medicinal product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the healthy volunteer or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol-mandated clinical laboratory tests and vital signs will be summarised in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated clinical laboratory values, vital signs and ECGs should therefore only be reported as AEs if they are clinically significant, fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational medicinal product, or require the healthy volunteer to receive specific corrective treatment.

If deterioration in a clinical laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational medicinal product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform appropriate AstraZeneca representatives **within 24 hours** of when he or she becomes aware of it.

The AstraZeneca representative will work with the Investigator to compile all the necessary information and ensure that all the necessary information is provided to Bristol-Myers Squibb Global Pharmacovigilance and Epidemiology within 1 calendar day of initial receipt for fatal and life threatening events and within three calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The completed report (including relevant CRF modules) is sent by fax to BMS Global Pharmacovigilance and Epidemiology, see Section 13.1.

The reference document for definition of expectedness/listedness for dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet is the IB. The reference documents for definition of expectedness/listedness for the marketed 5-mg dapagliflozin and 850-mg metformin Glucophage® are their respective Summaries of Product Characteristics.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (see Table 1).

The following laboratory variables will be measured:

Clinical chemistry	**Haematology**	**Urinalysis**
S-Alanine aminotransferase (ALT)	B-Haemoglobin	U-Glucose (dipstick)
S-Albumin	B-platelets	U-Protein (dipstick)
S-Alkaline phosphatase (ALP)	B-white blood cells	U-Red blood cells (dipstick)
S-Aspartate aminotransferase (AST)	B-Leukocyte differential count (absolute count):	U-white blood cells (dipstick)
S-Bilirubin, total		
S-Calcium	B-Basophils	**Drug screen**
S-Creatinine	B-Eosinophils	U-Amphetamine
S-Potassium	B-Lymphocytes	U-Benzodiazepine
S-Sodium	B-Monocytes	U-Cannabinoid
S-Glucose[a]	B-Neutrophils	U-Cocaine
		U-Opiates
Endocrinology	**Coagulation[c]**	**Serology[c]**
S-FSH[b]	P-Prothrombin time	Anti HIV1/HIV2
	P-Activated partial thromboplastin (APT) time	HBsAg
Pregnancy test[d]		Anti-HCV
U-hCG		

Anti-HCV=Anti-hepatitis C virus; B=Blood; HBsAg=Hepatitis B surface antigen; P=Plasma; S=Serum; U=Urine; U-hCG=urine human chorionic gonadotropin.

[a] Fasted samples at screening and admission
[b] At screening postmenopausal females only
[c] At screening only
[d] Female volunteers only

Urine pregnancy tests (females) will be performed at screening and upon admission (Day -1) at Visits 2 to 5. If a healthy volunteer tests positive to any of the predose tests they will be excluded from the study.

Samples with laboratory values outside the reference ranges suspected to be of any clinical significance will be retaken. Healthy volunteers, in whom suspected clinical significance is confirmed, will either not be included or, if already randomised, will be followed until normalisation or for as long as the Investigator considers it necessary. Additional laboratory values may be performed for safety reasons if judged appropriate by the Investigator.

Samples will be collected in tubes according to standard practices. The safety laboratory samples will be analysed using routine methods at Quintiles Drug Research Unit at [redacted]. The urinalysis will also be performed at the study centre according to local procedures.

For blood volumes see Section 7.1.

6.4.6 Physical examination

A complete physical examination will be performed at screening and at the follow-up visit and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculoskeletal (including spine and extremities) and neurological systems.

On admission, ie, on Day -1 at Visits 2 to 5, only a brief physical examination is required.

Height will be measured in centimetres and weight in kilograms. Measurements should be taken without shoes.

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

At enrolment (Visit 1) and follow-up (Visit 6), 12-lead paper ECGs will be obtained after 10 minutes supine rest (Table 1). The date, time and whether the ECG was normal or abnormal, as well as reason for abnormalities will be recorded. All ECGs will be evaluated by the Investigator, or, if necessary, a qualified cardiologist, who will judge the overall interpretation as normal or abnormal. If abnormal, a decision will be made on whether or not the abnormality is clinically significant.

QTcF will be recorded at screening. Clinical judgements will be included for abnormal recordings.

The Investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Supine blood pressure and pulse will be measured using a semi-automated BP after 10 minutes rest (sitting or supine) on a bed. For timings of assessments refer to the Study Plan (Table 1).

6.5 Pharmacokinetics

6.5.1 Collection of samples

Venous blood samples (6 mL) for determination of concentrations of dapagliflozin and metformin in plasma will be taken at the times presented in the Study Plan (Table 1).

Samples will be collected labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

6.5.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by Atlanbio, [redacted], [redacted] on behalf AstraZeneca, using validated analytical methods. The lower limit of quantification (LLOQ) of dapagliflozin in plasma is 0.200 ng/mL and the LLOQ of metformin in plasma is 2.00 ng/mL.

6.6 Pharmacodynamics

Not applicable.

6.7 Pharmacogenetics

Not applicable.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each healthy volunteer in this study is as follows:

Table 2 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	4	6	24
	Haematology	4	6	24
	Coagulation	3	1	3
	Serology	4	1	4
Endocrinology	FSH[a]	4	1	4
Pharmacokinetic		6	88	528
Total				587

[a] Postmenopausal females

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on dapagliflozin and/or metformin become available. However, the maximum volume to be drawn from each healthy volunteer will not exceed 650 mL.

7.2 Handling, storage and destruction of biological samples

7.2.1 Pharmacokinetic samples

Samples will be disposed of after the CSR has been finalised.

7.2.2 Safety samples

Details of the disposal of safety samples are provided in the Laboratory Manual.

7.3 Labelling and shipment of biohazard samples

The Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the healthy volunteer unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The PI keeps full traceability of collected biological samples from the healthy volunteer while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a healthy volunteer withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the healthy volunteer is withdrawn from further study participation.

The PI will:

- Ensure healthy volunteers' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensure that biological samples from that volunteer, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensure the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensure that the healthy volunteer and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference of Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The Informed Consent Form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the healthy volunteers. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any healthy volunteer into the study.

The EC should approve all advertising used to recruit healthy volunteers for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC annually.

Before enrolment of any healthy volunteer into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

8.4 Informed consent

The PI or delegate will:

- Ensure each healthy volunteer is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each healthy volunteer is notified that they are free to discontinue from the study at any time
- Ensure that each healthy volunteer is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each healthy volunteer provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the healthy volunteer
- Ensure that any incentives for healthy volunteers who participate in the study as well as any provisions for healthy volunteers harmed as a consequence of study participation are described in the ICF that is approved by an EC.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the PI and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised CSP).

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to EC see Section 8.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's EC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT

Quintiles will be managing the study on behalf of AstraZeneca.

9.1 Pre-study activities

Before the first healthy volunteer is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate healthy volunteers for the study
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca and the Investigator.

9.2 Training of study site personnel

Before the first healthy volunteer is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilised.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca/Quintiles representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the healthy volunteer's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating healthy volunteers. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the healthy volunteer's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the volunteer.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

The location of data identified as source will be provided in a source data identification document provided by Quintiles.

9.4 Study agreements

The PI at the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of volunteers and in all other respects, not relating to study conduct or treatment of volunteers, the terms of the CSA shall prevail.

Agreements between AstraZeneca and Quintiles should be in place before any study-related procedures can take place, or subjects are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last healthy volunteer undergoing the study'.

The study is expected to start in Q2 [redacted] and to end by Q3 [redacted]

The study may be terminated at individual centres if the study procedures are not being performed according to GCP or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin or metformin.

10. DATA MANAGEMENT BY QUINTILES

Data management will be performed by Quintiles Ltd, [redacted].

The data in this study will be collected using paper CRFs.

When the completed paper CRFs have been scanned and indexed, the data are entered into the study database and proofread.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by Quintiles Ltd, [redacted].

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated and signed the database will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

11. EVALUATION AND CALCULATION OF VARIABLES BY QUNITILES

11.1 Calculation or derivation of efficacy variable(s)

Not applicable.

11.2 Calculation or derivation of safety variable(s)

Adverse events will be collected for each healthy volunteer from the first administration of IMP (Day 1, Visit 2) until the follow-up visit (Visit 6). Serious AEs will be collected from when informed consent is obtained (Visit 1) until the follow-up visit (Visit 6). Summary statistics will be presented for the continuous safety variables.

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuation of IMP due to AEs. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the CPA Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory tests, vital signs and ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of patient reported outcome variables

Not applicable.

11.4 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed at Quintiles Inc, [redacted]. Quintiles Standard Operating Procedures (SOPs) and Work Instructions will be used as the default methodology if not otherwise specified. The actual sampling times will be used in the PK calculations. PK parameters will be derived using noncompartmental methods with WinNonlin® Professional Version 5.2, or higher, (Pharsight Corp., [redacted],

[redacted]). All PK computations will be performed using WinNonlin Professional 5.2, or higher; or SAS® Version 9.1, or higher (SAS Institute, Inc., [redacted]). Graphics may be prepared with SAS Version 9.1, or higher; or SigmaPlot® 9.0, or higher (Systat Software, Inc., [redacted]).

Any anomalous concentration values observed at the predose time point shall be identified in the PK analysis review documentation with a description of how the value was treated. If the anomalous predose concentration value is greater than 5% of the maximum observed concentration (C_{max}) in the profile, PK parameters for the profile will not be reported.

If data permits, the following single dose PK parameters will be determined for dapagliflozin and metformin:

C_{max}	Observed maximum analyte concentration, taken directly from the individual concentration-time curve.
t_{max}	Time to reach maximum analyte concentration, taken directly from the individual concentration-time curve.
t_{last}	Time of last quantifiable analyte concentration.
λ_z	Terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve.
$t_{½\lambda z}$	Terminal half-life, estimated by $(\ln 2)/\lambda_z$.
$AUC_{(0-t)}$	Area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration, calculated by linear up/log down trapezoidal summation.
AUC	Area under the plasma concentration-time curve from time zero extrapolated to infinity. AUC is estimated by $AUC_{(0-t)} + C_{last}/\lambda_z$ where C_{last} is the last observed quantifiable analyte concentration.
$\%C_0/C_{max}$	Percent of predose concentration relative to C_{max}
$\%AUC_{(0-t)}/AUC$	Percent of the area measured by $AUC_{(0-t)}$ relative to the extrapolated total AUC.

Additional calculations may be performed at the discretion of the PK scientist as appropriate.

The following PK diagnostic parameters will be calculated and listed but not summarised:

- The t_lower and t_upper of the log-linear regression to determine $t_{½\lambda z}$.
- Number of data points ($t_{½}$, N) included in the log-linear regression analysis.
- Goodness of fit statistic, R-Squared, for calculation of λ_z [Rsq].
- Percentage of AUC obtained by extrapolation ($\%AUC_{ex}$).

Additional PK parameters may be calculated if deemed appropriate.

All concentration and PK parameters will be presented according to Health Canada's Guidance Document, "Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A." (For details, refer to: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/gd_cbs_ebc_ld-eng.php)

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	4	6	24
	Haematology	4	6	24
	Coagulation	3	1	3
	Serology	4	1	4
Endocrinology	FSH[a]	4	1	4
Pharmacokinetic		6	88	528
Total				583 (587)

Comment [sw1]: 587 is correct. What does 583 represent? Which value can vary?

11.5 Calculation or derivation of pharmacodynamic variable(s)

Not applicable.

11.6 Calculation or derivation of pharmacogenetic variables

Not applicable.

11.7 Calculation or derivation of health economic variables

Not applicable.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY QUINTILES

12.1 Description of analysis sets

12.1.1 Safety analysis set

All healthy volunteers who received at least one dose of randomised IMP, and for whom any postdose data are available will be included in the safety population. Throughout the safety results sections, erroneously treated healthy volunteers (eg, those randomised to treatment A but actually given Treatment B) will be accounted for in the actual treatment group.

12.1.2 Pharmacokinetic analysis set

The PK analysis set will include all healthy volunteers who received at least 1 dose of IMP and who have sufficient PK data to evaluate any of the primary outcome variables (AUC, $AUC_{(0-t)}$ or C_{max}) and have no major protocol deviations or violations affecting the integrity of the PK data. Data from healthy volunteers who experience emesis at or before 2 times median t_{max} will only be listed and not be included in any statistical analysis.

A strategy for dealing with data affected by protocol violations and deviations will be agreed by the study team physician, pharmacokineticist, and statistician, prior to clean file and code break. Healthy volunteers will be analysed according to the treatment they actually received.

12.2 Methods of statistical analyses

The statistical analyses will be performed by Quintiles Inc, [redacted] by using SAS, version 9.1 or later. Quintiles SOPs and Work Instructions will be used as the default methodology if not otherwise specified.

Data will be presented by treatment. Missing data will result in a reduced sample size for that parameter. No action will be taken to handle missing data.

A healthy volunteer who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

Plasma concentrations and derived PK parameters will be reported to 3 significant figures; standard deviation will be reported to 4 significant figures and CVs will be presented to 1 decimal place. For all other data types, mean, median, minimum and maximum values will be reported to the same degree of precision as the raw data and the standard deviation will be reported to one further degree of precision. Percentage frequencies will generally be presented to the nearest integer. For derived data, rounding should be applied after calculations have been performed.

The primary objectives of this study are to demonstrate bioequivalence of a dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet relative to 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by SA) tablets administered together in the fasted state and to demonstrate the bioequivalence of a dapagliflozin/metformin (5 mg/850 mg) IR FDC tablet relative to 5-mg dapagliflozin and 850-mg Glucophage® (marketed in Canada by SA) tablets administered together in the fed state. These analyses will be performed using the nominal drug dose and corrected for the measured potency of the administered formulations.

In the fasted condition, point estimates and 90% confidence intervals for C_{max}, $AUC_{(0-t)}$, and AUC will be calculated for the Treatment B to Treatment A ratios of geometric means of dapagliflozin and metformin using a linear mixed effect model. In the fed condition, point estimates and 90% confidence intervals for C_{max}, $AUC_{(0-t)}$, and AUC will be calculated for the Treatment D to Treatment C ratios of geometric means of dapagliflozin and metformin using a linear mixed effect model. These estimates will be constructed from the results of fitting the linear mixed effect models for log-transformed data with treatment sequence and period as

fixed effects and subject within sequence as a random effect. All statistical comparisons will be made from this same model. Point estimates of the ratios and their confidence intervals will then be transformed back to original scale in order to give point estimates for the ratios of geometric means and their confidence intervals.

Bioequivalence will be concluded if the test-to-reference ratios of geometric means are contained within 0.80 to 1.25 for dapagliflozin and metformin AUC, $AUC_{(0-t)}$ and C_{max}. No adjustments will be made for multiplicity.

To look at fed versus fasted for the dapagliflozin/ metformin (5 mg/850 mg) IR FDC tablet, point estimates and 90% confidence intervals for C_{max}, $AUC_{(0-t)}$, and AUC will be calculated for the Treatment D to Treatment B ratios of geometric means of dapagliflozin and for metformin using a linear mixed effect model. These estimates will be constructed from the results of fitting the linear mixed effect models for log-transformed data with treatment and period as fixed effects and subject within sequence as a random effect. Point estimates of the differences and their confidence intervals will then be transformed back to original scale in order to give point estimates for ratios of geometric means in the original scale.

A secondary analysis will be performed if the C_0/C_{max} ratio is greater than 5% and/or the $AUC_{(0-t)}$/AUC ratio is less than 80%. Any volunteers who fall within either category will be excluded from the dataset, and a secondary analysis will be repeated.

No treatment comparisons will be made between Treatment A and Treatments C and D; nor between Treatment B and Treatment C.

The bioequivalence analyses will (if applicable) also be performed on the PK parameters corrected for the actual drug content of each of the formulations (potency-corrected analysis). See below examples of the methods of calculating the AUC, $AUC_{(0-t)}$ and C_{max} ratio estimates and their confidence limits, based on data corrected for measured content. The whole analysis need not be repeated; but only the corrected estimates need to be given.

Table 3 Estimates based on correction for measured content (example)

	Test Formulation	**Reference Formulation**
Lot number	EX109	40904
Expiry date	06/89	05/89
Date of analysis	01/04/88	01/04/88
Measured content (% of label claim)	95.4	99.3
Correction factors		
- raw scale-multiply	1.0482	1.0070
- log scale-add	0.0471	0.0070

AUC ratio and C_{max} ratio – calculations (example)

Based on measured contents in the example above, the following factor is obtained:

ln (99.3/95.4) = 0.04, which is to be added to the estimates on the ln scale.

Therefore:

AUC ratio = $e^{(-0.13 + 0.04)}$*100% = 91%

Lower limit = 100*$e^{(-0.13 + 0.04 - 1.761 * 0.0955)}$ = 77%

Upper limit = 100*$e^{(-0.13 + 0.04 + 1.761 * 0.0955)}$ = 108%

C_{max} ratio = $e^{(-0.21 + 0.04)}$ = 84%

Lower limit = 100*$e^{(-0.21 + 0.04 - 1.761 * 0.1600)}$ = 64%

Upper limit = 100*$e^{(-0.21 + 0.04 + 1.761 * 0.1600)}$ = 112%

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A listing of all concentration-time data for each treatment will be presented. Pharmacokinetic variables (dapagliflozin and metformin plasma concentrations and PK parameters) will be summarized by treatment using appropriate descriptive statistics, eg n, arithmetic mean, standard deviation (SD), geometric mean, geometric coefficient of variation (CV%), minimum (min), median, maximum (max). The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where *s* is the SD of the data on a log scale. For t_{max} and t_{last} only n, median, min and max will be used.

Plasma concentrations that are below the LLOQ will be handled as follows:

- At a time point where at least 1 value is above LLOQ, but less than 50% values are LLOQ, all values below LLOQ are set to LLOQ and a mean (arithmetic and geometric) value and SD and CV (coefficient of variation) are calculated.
- At a time point where more than half of the observations are below LLOQ only individual values are reported; mean, SD, geometric mean and CV% will be set to NQ. The minimum (min) value and the median are set to less than LLOQ.
- If all values are below LLOQ at any time point no descriptive statistics are calculated for that time point. Write NA (not applicable) in the field for standard deviation and CV% and write less than LLOQ in fields for mean, geometric mean, min, median and max in the table.
- The number of observations greater than LLOQ [number of observations above LLOQ (N>LLOQ)] will be reported in the table.

Quintiles global SOPs will be followed for the rounding conventions.

Figures of arithmetic mean concentration-time data will be presented on linear and semi-logarithmic scales by treatment. Individual concentration-time data will be graphically presented on linear and semi-logarithmic scales, with the semi-log plot presenting the regression line from which λ_z was estimated. Graphical presentations of PK data may be added at the discretion of the PK scientist.

Frequency distributions of gender and race will be tabulated by treatment. Summary statistics for age, body weight, height, and BMI will be tabulated by treatment.

All recorded AEs will be listed and tabulated by system organ class, preferred term and formulation. Vital signs and clinical laboratory test results will be listed and summarized by formulation. Any significant physical examination findings, ECG results, and clinical laboratory results will be listed.

12.3 Determination of sample size

Dapagliflozin

Assume there is no difference between the bioavailabilities of dapagliflozin from the 5-mg dapagliflozin/850 mg metformin FDC tablet versus dapagliflozin from co-administration of a 5-mg dapagliflozin tablet and an 850-mg Glucophage (marketed in Canada by SA) tablet under both fasted and fed conditions,

From Study D1691C00002, C_{max}, $AUC_{(0-t)}$, and AUC are log normally distributed with intra-subject standard deviations of 0.286, 0.081, and 0.093 for $\log(C_{max})$, $\log[AUC_{(0-t)}]$, and log[AUC], respectively.

Using a 90% power and a 2-sided alpha of 5%, there will need to be 3 healthy volunteers per treatment sequence, 12 healthy volunteers total, to conclude bioequivalence with respect to $AUC_{(0-t)}$ and AUC.

Using a 95% power and a 2-sided alpha of 5%, there will need to be 3 healthy volunteers per treatment sequence, 12 healthy volunteers total, to conclude bioequivalence with respect to $AUC_{(0-t)}$ and AUC.

If there is a 5% difference between the treatments, using a 90% power and a 2-sided alpha of 5%, there will need to be 3 healthy volunteers per treatment sequence, 12 healthy volunteers total, to conclude bioequivalence with respect to $AUC_{(0-t)}$ and AUC.

Assuming there is no difference in the C_{max} between the 2 treatments, there will need to be 7 healthy volunteers per treatment sequence, 28 healthy volunteers total, to have a 95% probability of the measured C_{max} of the test to reference product to be between 80% and 125%.

If there is a 5% difference between treatments for C_{max}, there will need to be 8 healthy volunteers per treatment sequence, 32 healthy volunteers total, to have a 95% probability of the measured C_{max} of the test to reference product to be between 80% and 125%.

Metformin

Assume there is no difference between the bioavailabilities of metformin from the 5 mg dapagliflozin/850 mg metformin FDC tablet versus dapagliflozin from coadministration of a 5-mg dapagliflozin tablet and an 850-mg Glucophage (marketed in Canada by SA) tablet under both fasted and fed conditions.

From saxagliptin Study CV181081, C_{max}, $AUC_{(0-t)}$, and AUC are log normally distributed with intra-subject standard deviations of 0.220, 0.180, and 0.174 for log(C_{max}), log[$AUC_{(0-t)}$], and log[AUC], respectively.

Using a 90% power and a 2-sided alpha of 5%, there will need to be 5 healthy volunteers per treatment sequence, 20 healthy volunteers total, to conclude bioequivalence with respect to $AUC_{(0-t)}$ and AUC.

Using a 95% power and a 2-sided alpha of 5%, there will need to be 6 healthy volunteers per treatment sequence, 24 healthy volunteers total, to conclude bioequivalence with respect to $AUC_{(0-t)}$ and AUC.

If there is a 5% difference between the treatments, using a 90% power and a 2-sided alpha of 5%, there will need to be 6 healthy volunteers per treatment sequence, 24 healthy volunteers total, to conclude bioequivalence with respect to $AUC_{(0-t)}$ and AUC.

Assuming there is no difference in the C_{max} between the two treatments, there will need to be 4 healthy volunteers per treatment sequence, 16 healthy volunteers total, to have a 95% probability of the measured C_{max} of the test to reference product to be between 80% and 125%.

If there is a 5% difference between treatments for C_{max}, there will need to be 5 healthy volunteers per treatment sequence, 20 healthy volunteers total, to have a 95% probability of the measured C_{max} of the test to reference product to be between 80% and 125%.

At least 36 healthy volunteers will be enrolled to ensure that 32 healthy volunteers complete the study. A maximum of 40 healthy volunteers may be enrolled.

The sample size was selected to be consistent with the research hypothesis as described in Section 1.2.

12.4 Data monitoring committee

Not applicable.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the Investigator may contact the CPA physician. If the CPA physician is not available, contact the CPA program director at AstraZeneca.

Name	Role in the study	Address & telephone number
[redacted]	CPA Physician	AstraZeneca R&D [redacted]
[redacted]	CPA Program Director	AstraZeneca R&D [redacted]
	Pharmacovigilance	Bristol-Myers Squibb Global Pharmacovigilance and Epidemiology [redacted] E-mail: [redacted]
	24-hour emergency cover at central R&D site	E-mail: [redacted]
[redacted], MBBS	Principal Investigator	Quintiles Drug Research Unit a[redacted] Quintiles Ltd, [redacted]

Name	Role in the study	Address & telephone number
[redacted]	Quintiles Project Manager	Quintiles Drug Research Unit [redacted], Quintiles Ltd, [redacted]

13.2 Overdose

An overdose is defined as the accidental or unintentional ingestion of any dose of IMP that is considered both excessive and medically important. Dapagliflozin has been well tolerated at doses of up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dosing testing for 14 days in healthy volunteers and patients with T2DM. Once an Investigator decides that a particular occurrence is an overdose, it must be reported as an SAE, see Section 6.4.4. If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed.

13.3 Pregnancy

Females and female partners of male volunteers who are premenopausal or not surgically sterile should use adequate birth control during the study. Should a pregnancy still occur, the IMP should be discontinued immediately and the study monitor should be informed. The pregnancy report module in the CRF should be completed by the Investigator, and the study monitor will forward the information to BMS using the same procedure as for SAE reporting (Section 6.4.4). The outcome of each pregnancy will also be collected once this information is available.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the volunteer was discontinued from the study.

14. LIST OF REFERENCES

Not applicable.