Clinical Study Protocol

Drug Substance	Dapagliflozin
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A two part, open label, randomized, single-centre, phase I bioequivalence study comparing (Part I) the fixed dose combination 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 fixed dose combination 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

Sponsor:

AstraZeneca AB, SE-151 85 Södertälje, Sweden

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 two part, open label, randomized, single-centre, phase I bioequivalence study comparing (Part I) the fixed dose combination 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 fixed dose combination 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

Principal Investigator

Study centre and number of subjects planned

This study will be conducted at International GmbH, Berlin, Germany. The planned number of randomised healthy volunteers per part is 60 healthy volunteers. The enrolment period will be 19 days.

Study period	Phase of development
Estimated date of first healthy volunteer enrolled	I
Estimated date of last healthy volunteer completed	

Objectives

Primary objectives

Part I: To establish the bioequivalence of a newly formulated fixed dose combination dapagliflozin/metformin immediate-release (IR) tablet (2.5 mg/850 mg) to the individual dapagliflozin tablet (2.5 mg) and individual metformin IR tablet (850 mg) co-administered.

Part II: To establish the bioequivalence of a newly formulated fixed dose combination dapagliflozin/metformin IR tablet (5 mg/1000 mg) to the individual dapagliflozin tablet (5 mg) and individual metformin IR tablet (1000 mg) co-administered.

Secondary objective

To examine the safety and tolerability of the combination of dapagliflozin and metformin.

Study design

This study is a single-centre, two parts, randomized, open label, crossover bioequivalence study. The first part is a two-way crossover comparing the newly formulated fixed dose combination (FDC) dapagliflozin/metformin IR (2.5 mg/850 mg) tablet to the individual dapagliflozin and metformin IR tablets administered together. The second part is a two-way crossover comparing the newly formulated FDC dapagliflozin/metformin IR (5 mg/1000 mg) tablet to the individual dapagliflozin and metformin IR tablets administered together. Parts I and II are independent of each other, and may be carried out simultaneously. Healthy volunteers participating in Part I will not be enrolled in Part II. Healthy volunteers participating in Part II will not be enrolled in Part I.

Target subject population

Healthy male and female volunteers aged 18 to 45 both inclusive. Female subjects must be non-fertile or must be abstinent during the study.

Investigational product, dosage and mode of administration

Fixed dose combination (FDC) dapagliflozin/metformin of 2.5 mg /850 mg (Part I) and FDC dapagliflozin/metformin of 5 mg /1000 mg (Part II).

Comparator, dosage and mode of administration

Part I: 1 tablet of dapagliflozin 2.5 mg and 1 tablet of metformin IR 850 mg

Part II: 1 tablet of dapagliflozin 5 mg and 1 tablet of metformin IR 1000 mg

Duration of treatment

Part I: Each healthy volunteer will receive one single dose of FDC dapagliflozin/metformin of 2.5 mg /850 mg and each one single dose of dapagliflozin 2.5 mg and metformin 850 mg. Wash-out period will be at least 7 days.

Part II: Each healthy volunteer will receive one single dose of FDC dapagliflozin/metformin of 5 mg /1000 mg and each one single dose of dapagliflozin 5 mg and metformin 1000 mg. Wash-out period will be at least 7 days.

Outcome variables:

- Pharmacokinetics

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), Area under the plasma concentration-time curve from zero to infinity (AUC_{inf}), Area under the plasma concentration-time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and terminal half-life ($t_{1/2}$) of dapagliflozin and metformin

- Safety

  Adverse events and laboratory variables

Statistical methods

The primary objectives of this study are to demonstrate bioequivalence for newly formulated FDC tablets versus the individual dapagliflozin and metformin IR tablets (free combination) of dapagliflozin/metformin 2.5 mg/850 mg and for 5 mg/1000 mg. For both objectives, bioequivalence will be demonstrated if the 90% confidence interval (CI) for the formulation effect is contained within the interval of 0.8000-1.2500 for $AUC_{(0-t)}$, AUC_{inf} and C_{max} with respect to both dapagliflozin and metformin.

The study has two parts: Part I is 2-treatment, 2-period, crossover design to evaluate bioequivalence for the 2.5 mg/850 mg formulation and Part II is a 2-treatment, 2-period, crossover design to evaluate bioequivalence for the 5 mg/1000 mg formulation. In Part I, subjects will be randomized to one of two sequences in a 1:1 allocation. Sequence 1 will administer the FDC in period 1 and the free combination in period 2. Sequence 2 will administer the treatments in the reverse order. For Part II, subjects will be randomized in the same way as in Part I.

$AUC_{(0-t)}$, AUC_{inf} and C_{max} will be log-transformed prior to analysis. All endpoints will be analyzed using an analysis of variance (ANOVA) model for each part separately, with sequence, period and formulation as fixed effects and subject within sequence as a random effect. The results of the analysis will be presented in terms of the estimated geometric mean for each formulation with corresponding 95% confidence interval, and the estimated formulation effect (ratio of geometric means) with a 90% confidence interval. Geometric means will be estimated by back-transformation of least squares means from the log-transformed data with adjustment for any imbalances in the design. All other pharmacokinetic parameters will be summarized by formulation using descriptive statistics only.

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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.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in section 6.3.1)
ANOVA	Analysis of Variance
AUC_{inf}	Area under plasma concentration-time curve from zero to infinity [amount•time/volume]
$AUC_{(0-t)}$	Area under the curve from time zero to last concentration measured
BMI	Body mass index
BMS	Bristol-Myers Squibb
BP	Blood pressure
C_{max}	Maximum plasma concentration
CRF	Case Report Form
CS	Cardiosoft®
DMP	Data Management Plan
DVS	Data verification specification
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic data capture
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FDC	Fixed dose combination
GCP	Good Clinical Practice
GEMS	General Electrics Medical Systems
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IB	Investigator's brochure
IP	Investigational Product
IR	Immediate-release
LOQ	Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MSE	Mean square error
OAE	Other Significant Adverse Event (see definition in section 11.1.1)
pCRF	paper Case Report Form
PK	Pharmacokinetic
SAE	Serious adverse event (see definition in section 6.3.2)
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard deviation
SOP	Standard operating procedure
SGLT2	Human renal sodium-glucose cotransporter
T2DM	Type 2 Diabetes Mellitus
t_{max}	Time to maximum plasma concentration
$t_{1/2}$	Elimination half life

1. INTRODUCTION

1.1 Background

1.1.1 Dapagliflozin

Dapagliflozin is a rationally designed, potent, highly selective and orally active 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 by promoting its urinary excretion. Traditionally, the presence of glucose in the urine of diabetes patients has been seen as a sign of poor glycemic control and thus something to be avoided. However, familial renal glucosuria in humans, due to genetic mutations that reduce the function of SGLT2, is associated with life-long glucosuria, which is generally asymptomatic Hans et al 2008, Matthei et al 2000. Results from nonclinical studies and completed clinical studies suggest that dapagliflozin intentionally promotes the urinary excretion of glucose as a safe and effective method of reducing blood glucose levels. Chronic correction of hyperglycaemia by SGLT2 inhibitors has also been shown to improve overall glucose utilization and reduce hepatic glucose production in pre-clinical models Hans et al 2008, Komoroski et al 2009, Matthei et al 2000.

1.1.2 Metformin

Metformin hydrochloride is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Metformin hydrochloride may act via 3 mechanisms: either (1) by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, or (2) by increasing insulin sensitivity in muscle improving peripheral glucose uptake and utilisation, or (3) by a delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters known to date. Metformin does not have any effect n the total glucose. It is suggested that the decrease of total glucose is based on an improved glycaemic control and not due to a direct effect. In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: Metformin hydrochloride reduces total cholesterol, low density lipoprotein cholesterol and triglyceride levels.

Gastrointestinal disturbances (diarrhoea, nausea, vomiting, and abdominal bloating) are the most common adverse reactions to metformin.

1.2 Research hypothesis

The hypotheses are

1. that the fixed dose combination (FDC) 2.5 mg/850 mg

and

2. that the FCD 5 mg/1000 mg tablets

are bioequivalent to the individual tablets when co-administered as demonstrated by C_{max}, AUC_{inf} and $AUC_{(0-t)}$ for each of dapagliflozin and metformin, respectively.

1.3 Rationale for conducting this study

According to the requirements of the European Medicines Agency (EMEA) and Food and Drug Administration (FDA), bioequivalence testing is required for all new formulated FDC drugs. Currently the clinical development of dapagliflozin has reached the Phase III clinical studies.

To reach a maximum treatment effect in T2DM patients, often a combination of antidiabetic drugs is required. In order to enhance patient convenience and compliance, it is intended to provide physicians/patients with 2.5 mg/850 mg and 5 mg/1000 mg dapagliflozin/ metformin IR tablets. Two formulations, one with a lower and one with a higher amount of dapagliflozin and metformin, respectively, will appropriately complete the existing range of formulations.

1.4 Benefit/risk and ethical assessment

Dapagliflozin's novel mechanism of action, inhibition of SGLT2, can result in lowering plasma glucose regardless of the patient's insulin sensitivity and β-cell functional secretory status. Because the mechanism is independent of insulin secretion or insulin action, this approach to antidiabetic therapy provides an opportunity to achieve clinically important glycaemic efficacy with a relatively low risk of hypoglycaemia. 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 risk of hypoglycaemia is inherently low because of the insulin independent mode of action. In addition, increased excretion of glucose may promote weight loss or prevent weight gain, a potential benefit for many patients with T2DM.

The inhibition of SGLT2 results in increased urinary glucose concentrations, which may lead to an increased risk of developing urinary tract infections (UTIs) and myotic infections. Neither UTIs nor myotic infections were reported in clinical Phase-I studies, however in clinical Phase-III studies, patients receiving dapagliflozin showed an increased frequency of UTIs and myotic infections when compared to placebo.

Based on the mechanism of action of dapagliflozin and results of animal and clinical studies, there may be a potential risk for this compound to cause hypovolemia or electrolyte imbalance. As a precaution, subjects at risk for hypovolemia or electrolyte disturbance should not receive dapagliflozin until more clinical information is available from human studies. In subjects already receiving dapagliflozin who develop conditions that may cause hypovolemia or electrolyte imbalance, decisions to interrupt or discontinue dapagliflozin therapy and management of subjects should be based on clinical judgment.

Neither dapagliflozin nor metformin showed any changes in their Pharmacokinetic (PK) profile when administered together as when administered alone (refer to Investigator's brochure [IB]).

Imbalances of liver function test parameters in Phase 3 studies were observed with diabetic patients in some but not all studies. There were no marked abnormalities reported for alkaline phosphatase or total bilirubin >2x upper limit of normal. All elevations have been reversible except a few with a clear non-drug cause, for instance in patients with a pancreatic cancer. The enzyme elevations have not showed any specific pattern with regards to exposure time, but several of them had appeared at more than 3 months of exposure.

While dietary and lifestyle interventions remain the fundamental approach to the treatment of T2DM, a large number of patients require daily administration of multiple pharmacologic agents to achieve adequate glycaemic control (HbA1c <7.0 %). T2DM is a progressive disease characterized by worsening glycaemic control over the years in spite of adequate treatment with metformin, a sulfonylurea or a thiazolidinedione drug (Kahn et al 2006). A FDC therapy with dapagliflozin and metformin for use as an adjunct to diet and exercise to improve glycaemic control in patients with T2DM who are inadequately controlled on their maximal dose of metformin or in patients already treated with the combination of dapagliflozin and metformin will be a significant addition to the efficacy of drug therapy, with the added advantage of improved compliance and convenience. Adequate glycaemic control has been shown to prevent complications from T2DM in particular microvascular complications such as retinopathy, neuropathy and nephropathy, each with potentially serious consequences for the individual patient concerned.

2. STUDY OBJECTIVES

2.1 Primary objective

Part I

To establish the bioequivalence of a newly formulated fixed dose combination dapagliflozin/metformin immediate-release (IR) tablet (2.5 mg/850 mg) to the individual dapagliflozin tablet (2.5 mg) and individual metformin IR tablet (850 mg) co-administered.

Part II

To establish the bioequivalence of a newly formulated fixed dose combination dapagliflozin/metformin IR tablet (5 mg/1000 mg) to the individual dapagliflozin tablet (5°mg) and individual metformin IR tablet (1000 mg) co-administered.

2.2 Secondary objectives

To examine the safety and tolerability of the combination of dapagliflozin and metformin.

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

This study is a single-centre, two parts, randomized, open label, crossover bioequivalence study. The first part is a two-way crossover comparing the newly formulated FDC dapagliflozin/metformin IR (2.5 mg/850 mg) tablet to the individual dapagliflozin and metformin IR tablets administered together. The second part is a two-way crossover comparing the newly formulated FDC dapagliflozin/metformin IR (5 mg/1000 mg) tablet to the individual dapagliflozin and metformin IR tablets administered together. See also Figure 1 and Figure 2. Parts I and II are independent of each other, and may be carried out simultaneously.

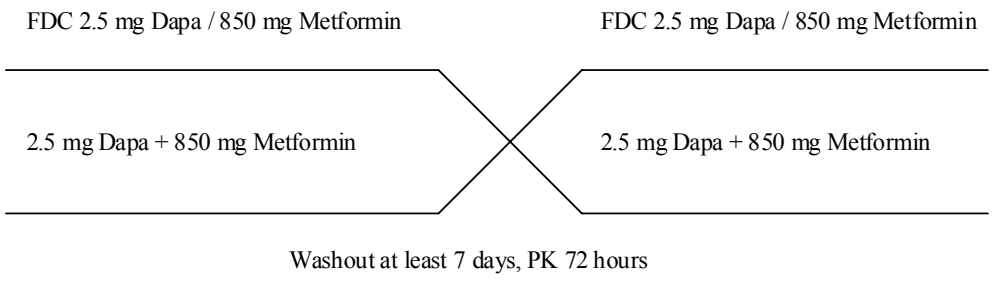
A total of 120 male and non-fertile female healthy volunteers will be included in this study with 60 in each study part. Healthy volunteers participating in Part I will not be enrolled in Part II. Healthy volunteers participating in Part II will not be enrolled in Part I.

All treatments will be administered to the healthy volunteers in the fed state.

In Part I, healthy volunteers will be randomized to one of two sequences in a 1:1 allocation. Sequence 1 will administer the FDC in period 1 and the free combination in period 2. Sequence 2 will administer the treatments in the reverse order. For Part II, healthy volunteers will be randomized in the same way as in Part I.

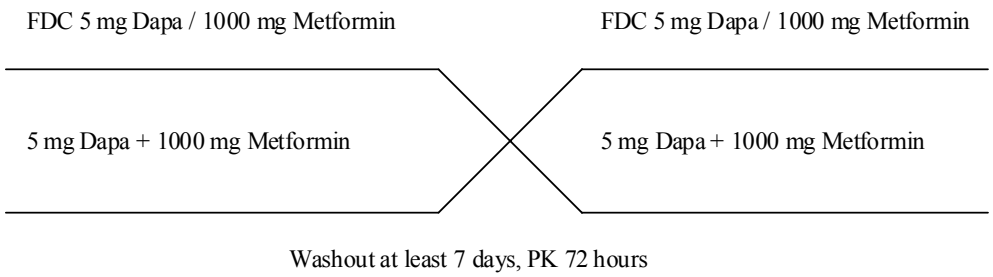
An enrolment examination for eligibility will be performed within 19 days before the dosing. Randomization will take place immediately before the first dosing. The wash-out period between both dosing periods will be at least 7 days. Following last dosing, a follow-up examination will be performed at least 6 days after the last PK sample 72 hours post-dose has been taken. The overall duration for each subject will be approximately 38 days.

Figure 1 Part I (2.5 mg + 850 mg)



FDC=Fixed dose combination, PK=pharmacokinetic, Dapa = Dapagliflozin

Figure 2 Part II (5 mg + 1000 mg)



FDC=Fixed dose combination, PK=pharmacokinetic, Dapa = Dapagliflozin

3.1 Overall study design and flow chart

Table 1 Study Flow Chart

	Enrolment	Visits for each period *				Follow-up[a]
Visit No	**1**	**2 and 3**				**4**
Day No	**–19 to -2**	**–1**	**1**	**2**	**3**	**4**	**At least 6 days after last PK sample**
Signed Informed Consent Form	X						
In-house		X	X	X	X	X	
Ambulant	X						X
Inclusion/exclusion criteria	X	X					
Demographics	X						
Physical examination	X					X	X
Weight and height[a]	X						X
Medical and surgical history	X						
Serology (HbsAg, HCV Ab, HIV-1/2 Ab)	X						
Urine drug screen	X	X					
Alcohol urine test	X	X					
Vital signs (including body temperature)[b]	X	X	X	X	X	X	X
12-lead ECG	X						X
Safety laboratory (haematology, clinical chemistry, urinalysis)	X	X				X	X
Pregnancy test	X	X					

Table 1 Study Flow Chart

	Enrolment	Visits for each period *				Follow-up[a]
Visit No	**1**	**2 and 3**				**4**
Day No	**–19 to -2**	**–1**	**1**	**2**	**3**	**4**	**At least 6 days after last PK sample**
Randomisation (Visit 2) [c]			X				
IP administration			X				
PK blood sampling[d]			X	X	X	X	
AE[e]		X	X	X	X	X	X
SAE[f]	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X

Abbreviations: AE = Adverse event; ECG = Electrocardiogram, HBsAg = Hepatitis B surface antigen, HCAb = Hepatitis C antibody, HIV1/2 Ab = human immunodeficiency virus-1/2 antibodies; IP = Investigational product, PK = pharmacokinetic; SAE = Serious adverse event. *The wash-out period will be at least 7 days between the periods.

[a] Height will be assessed only at the enrolment visit (Visit 1).
[b] Vital signs will be obtained he volunteer in a supine position (resting in bed for at least 10 minutes).
[c] Just before dosing
d Collection of PK blood samples: for the time points visit 2-3 see Table 2.
[e] AEs will be recorded from first intake of IP in period 1 until Follow-up.
[f] SAEs will be collected from the time when informed consent is obtained until the end of study (including the Follow-up visit).

Table 2 Study plan

Visit	Day	Nominal Protocol Time	IP	PK in Blood	BP pulse	Safety laboratory	Other
2 and 3	1	pre-dose, –01:00 to –00:30			X		
		-00:30					Start of breakfast
		-00:05					End of breakfast
		pre-dose		1			
		00:00	X	–			
		00:15		2			

Table 2 Study plan

Visit	Day	Nominal Protocol Time	IP	PK in Blood	BP pulse	Safety laboratory	Other
		00:30		3			
		01:00		4			
		01:30		5			
		02:00		6			
		03:00		7			
		04:00		8			Lunch: not until 4 hours post-dose
		05:00		9			
		06:00		10			
		08:00		11			
		10:00					Dinner
		12:00		12			
		14:00					Sack
		16:00		13			
	2	24:00		14	X		
		30:00		15			
		36:00		16			
		42:00		17			
	3	48:00		18	X		
		54:00		19			
		60:00		20			
	4	72:00		21	X	X	

BP = blood pressure; PK = pharmacokinetic, IP = Investigational product,

3.2 Rationale for study design, doses and control groups

The chosen design of this study meets the requirements of the EMEA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). The proposed standard design with two treatments and two periods will be used per study part.

The doses of twice daily 2.5 and 5 mg dapagliflozin, used for the FDCs have been investigated in the phase IIa and the ongoing phase III program and were shown to be effective and has not raised any safety concern

The doses of twice daily 2.5 and 5 mg dapagliflozin used for these FDC formulations found to be sufficient to reach the expected therapeutic effect in patients with T2DM. The doses chosen for metformin are the doses commonly used for metformin in the treatment of T2DM.

4. SUBJECT SELECTION CRITERIA

Investigator should keep a record, the subject screening log, of subjects who entered pre-study screening.

Each healthy 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.

No gender-balanced inclusion of the healthy volunteers is required.

4.1 Inclusion criteria

For inclusion in the study subjects must fulfil the following criteria:

1. Give written informed consent

2. Healthy male and female subjects aged 18-45 years

3. Female healthy volunteers must be post-menopausal (cessation of menses >1year), be surgically sterile (documented) or hysterectomy or on abstinence

4. Have a body mass index (BMI) between 18 and 29.9 kg/m^2, inclusive

5. Have normal physical exam, vital signs Electrocardiogram (ECG) findings, and laboratory values (unless investigator considers laboratory abnormality to be not clinically significant)

6. Able to communicate with the investigator and the study staff.

4.2 Exclusion criteria

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

1. Use of prescription medication for a chronic or acute medical condition within 3 weeks of randomization

2. Use of over the counter preparations including herbal remedies, ST. John's Wort, ginseng, ginko, and vitamin preparations within 14 days of randomization unless approved by the sponsor and investigator

3. History or presence of neurologic, hematologic, psychiatric, gastrointestinal, hepatic or renal disease, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs as determined by the investigator

4. Symptoms of any clinically relevant illness within 3 weeks prior to randomization

5. History of surgery within 3 months prior to randomization unless approved by sponsor and investigator

6. History of symptomatic hypoglycaemia

7. History of allergy to metformin

8. History of substance abuse in the last year

9. Use of alcohol, within 7 days prior to admission to the clinical research unit

10. Use of tobacco or history of tobacco use in the 3 months prior to randomization

11. Positive test for Human immunodeficiency virus (HIV), hepatitis B surface antigen or hepatitis C antibody

12. Receipt of an investigational drug within 60 days prior to randomization

13. Positive urine drug screen including alcohol and cotinine

14. Previous participation in a clinical study with dapagliflozin (BMS-512148) and/or with any other SGLT2 inhibitor in which the patient received at least one dose of study medication

15. Previous participation in an AstraZeneca (AZ) or BristolMyers-Sqibb dapagliflozin study

16. Involvement in the planning and conduct of the study

17. Blood transfusion within 12 weeks of randomization

18. Donation of blood within 3 months or donation of plasma within 14 days prior to screening (Visit 1)

19. Consumption of Seville oranges or grapefruit within 1 week prior to randomization

20. Positive pregnancy test

21. Employees of the clinical research unit conducting the study

22. Subjects who, in the opinion of the investigator, should not participate in the study

23. Vulnerable persons.

Procedures for withdrawal of incorrectly enrolled subjects see section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

1. All healthy volunteers will be served standardized meals during the in-house periods at the early phase clinical unit, and no other foods will be permitted. The menus will be identical for visit 2 and 3. Copies of the menu will be provided to the sponsor.

2. On Day 1 of dosing at Visit 2 and 3, the subjects will fast for 8 hours overnight. Breakfast will be served 30 minutes prior to dosing of each subjects medication.

3. The pre-dose meal should be a standardized non-high fat meal (650 calories with about 30% of calories derived from fat). The composition of the meal should be described with regard to protein, carbohydrate, and fat content (specified in grams, calories and relative caloric content).

4. Water will be allowed ad lib except from 2 hours before until 2 hours after dose administration.

5. The drug product should be dosed with 240 mL of room temperature water.

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

7. Abstain from consuming any of the following.

8. Drugs of abuse during the entire study. In addition, poppy seeds (eg, on bread rolls) can give a positive signal for opiates and should not be ingested 72 hours before screening (Visit 1) until the end of the study.

9. Food and drink (except water) for at least 8 hours prior to safety laboratory measurements at screening (Visit 1) and follow-up (Visit 4).

10. Consuming grapefruit, grapefruit juice Seville oranges, or orange marmalade (made with Seville oranges) or other products containing grapefruit or Seville oranges beginning 7 days before screening (Visit 1) and during the study.

11. Liquorice containing products 24 hours prior to admission and during Visit 2 and 3. Alcohol from 72 hours before and during enrolment (Visits 1) and before admission and during Visit 2.

12. Caffeine-containing beverages and foods, eg, coffee, tea, chocolate, and soft drinks (eg, Red Bull) for 10 hours before drug administration.

13. Abstain from nicotine use and smoking throughout the entire study period until after the final medical examination at the study follow-up.

14. Abstain from taking any medication (prescribed or over the counter products, ie, including vitamins, herbal remedies eg, St John´s Wort and mineral supplements) from 2 weeks prior to admission (Visit 2) and during the clinical study except for any occasional use of paracetamol. However, this should not obviate necessary medical treatment. If any medication is necessary, it should be prescribed by the investigator and the AstraZeneca should be informed (section 5.6).

15. Subjects should abstain from strenuous physical activity that is not within the subject's normal weekly routine 5 days before screening (Visit 1) and after admission during Visit 2 and 3.

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

17. Male healthy volunteers should abstain from unprotected sex and sperm donation from the first administration of the investigational product (IP) until 3 months after the last administration of the IP. As a precaution, subjects will be advised to use condoms in addition to a reliable form of contraception, for the specified period.

5.2 Subject enrolment and randomisation

The Principal Investigator or designee will:

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

2. Assign potential subject a unique enrolment number, beginning with "E#" after signing the informed consent form.

3. Each subject will be assigned a identification number irrespective of eligibility.

4. Determine eligibility of the healthy volunteer. See sections 4.1 and 4.2.

5. The numbers will be sequential and rising starting with number "101" for Part I and "201" for Part II

6. Allocation to subject number will be performed at pre-dose of Period 1 in each study part.

If a healthy volunteer withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused and he/she cannot re-enter into the study. Healthy volunteers, who discontinue participation in the study after dosing, will not be replaced.

5.2.1 Procedures for randomisation

A randomisation scheme will be produced by AstraZeneca R&D using the global randomisation system. Randomisation codes will be assigned strictly sequentially as healthy volunteers become eligible for randomisation.

5.3 Procedures for handling incorrectly enrolled healthy volunteers

Healthy volunteers who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or randomised. There can be no exceptions to this rule.

Where healthy volunteers that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where healthy volunteers subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the healthy volunteer from treatment.

The AstraZeneca Study Delivery Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the healthy volunteer should have their study therapy stopped.

5.4 Blinding and procedures for unblinding the study (not applicable)

5.5 Treatments

5.5.1 Identity of investigational products

Table 3 Identity of the investigational products

Investigational product	Dosage form and strength	Manufacturer
Dapagliflozin/ Metformin	FDC tablet 2.5 mg/ 850 mg	AstraZeneca
Dapagliflozin/ Metformin	FDC tablet 5 mg / 1000 mg	AstraZeneca
Dapagliflozin	Tablet 2.5 mg	Bristol-Myers Squibb
Dapagliflozin	Tablet 5 mg	Bristol-Myers Squibb
Glucophage® (metformin hydrochloride)	Tablet 1000 mg	Merck
Glucophage® (metformin hydrochloride)	Tablet 850 mg	Merck

The investigational products (IP) will be supplied as study specific bulk supply by AstraZeneca, Pharmaceutical and Analytical R&D, Sweden.

Metformin will be supplied as commercially available metformin IR tablets (Glucophage®). The tablets will be packed in blisters.

The study site dispensary staff will dispense the IPs into individual subject labelled dose cups, according to the randomisation scheme, provided by AstraZeneca. The dose cups will be provided by AstraZeneca.

Primary packaging of dapagliflozin tablets will be carried out by Bristol-Myers Squibb or their designee in accordance with current Good Manufacturing Practice (GMP), and primary packaging of dapagliflozin/metformin IR tablets will be carried out by AstraZeneca in accordance with current GMP.

5.5.2 Doses and treatment regimens

The following doses will be administered in one of two fixed order sequences according to a randomization schedule:

Sequence 1 will administer the FDC in period 1 and the free combination in period 2. Sequence 2 will administer the treatments in the reverse order. For Part II, subjects will be randomized in the same way as in Part I.

All doses will be orally administered as single doses. The tablets should be swallowed together with 240 mL distilled water, the subject in upright position, in the morning of Day 1 of both treatment periods in both study parts. Investigational products administration will be supervised by study staff and will be followed by a mouth check.

5.5.3 Additional study drug (not applicable)

5.5.4 Labelling

The IPs will be labelled at Investigational Products (IPS), Pharmaceutical and Analytical R&D AstraZeneca, according to current European Union Good Manufacturing Practice (GMP) guidelines, Annex 13 and local regulatory requirements. The labels will fulfil GMP Annex13 requirements for labelling.

Dose cup labels will be provided by and study site dispensary staff will label the dose cups

5.5.5 Storage

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

The dispensing and retention of reserve samples of investigational product 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 paracetamol/acetaminophen and occasional use of nasal anticongestants no concomitant medication or therapy will be allowed. The healthy volunteers should be instructed that no other medication is allowed including herbal remedies, vitamin supplements, minerals and over-the-counter products without the consent of the investigator.

Medication, which is considered necessary for the healthy volunteer's safety and well-being, may be given at the discretion of the investigator during the residential period. When any medication is required, it should be prescribed by the investigator who should inform the AstraZeneca Study Team Physician. Following consultation with the Study Team Physician, the investigator should determine whether or not the healthy volunteer should continue in the study.

5.7 Treatment compliance

The administration of all medication (including investigational products) should be recorded in the appropriate sections of ClinBase™.

Treatment compliance will be assured by supervised administration of the investigational product by the investigator or delegate. The dose, date and time of administration of the investigational product will be recorded and checked by the monitor at monitoring visits.

5.7.1 Accountability

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

personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction of unused study drugs (excluding the amount of retention samples). The study personnel at are responsible for the retention of samples of the IPs. Certificates of delivery, destruction and return should be signed.

5.8 Discontinuation of investigational product

Healthy volunteers may be discontinued from investigational product (IP) in the following situations:

- Healthy volunteer decision. The healthy volunteer is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance to study protocol as judged by the investigator and/or AstraZeneca
- Incorrectly randomised healthy volunteers
- Healthy volunteer lost to follow-up.

Risk to healthy volunteers as judged by the investigator and /or AstraZeneca.

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

5.9 Withdrawal from study

Healthy volunteers are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such healthy volunteers will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see sections 6.3.3 and 6.3.4).

Healthy volunteers who are withdrawn from the study by the investigator due to Adverse Events (AEs) after dosing will not be replaced. Healthy volunteers who withdraw for any 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 these assessments are detailed in the study plan (see Table 1 and Table 2).

6.1 Recording of data

Electronic Case Report Forms (eCRFs) will be used to record all data not captured electronically at bedside (see section 6.1.1). Trained study site personnel will perform manual data entry and editing. The data entry screens used to capture the eCRF data will be designed according to the AstraZeneca Case Report Form (CRF) Standard.

In cases where electronic direct data entry is not possible, data will first be recorded on a paper CRF (pCRFs), medical journal or other source documents and thereafter entered into the clinical study database.

The Principal Investigator will provide AstraZeneca with all data produced during the study from the scheduled study assessments. He ensures the accuracy, completeness, legibility, and timelines of the data reported to AstraZeneca in ClinBase™ and in all required reports. For a more detailed description of the data flow, including electronic data capture, refer to section 10.

6.1.1 Electronic data capture at Early Phase Clinical Unit

During the study, data will be captured electronically at bedside using the electronic data capture (EDC) application ClinBase™.

The investigator will review and approve the electronically captured data before transferring the data to the clinical study database. Any changes made prior to investigator approval will be documented within the audit trail of the electronic data capture application. Any missing,

impossible, or inconsistent entries will be queried after transfer to the clinical study database, in accordance with practices.

6.2 Data collection and enrolment

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

Demographic data and other characteristics will be recorded and will include: year of birth, gender and race and other information.

Each healthy volunteer will undergo screening during the 19 days prior to admission to confirm eligibility. This will consist of:

1. A standard medical, medication and surgical history with review of the inclusion and exclusion criteria with the healthy volunteer

2. A complete physical examination

3. Height, weight and calculation of BMI

4. Vital signs – resting supine and standing blood pressure (BP), pulse

5. Recording a resting 12-lead standard ECG

6. A blood sample for routine clinical chemistry, haematology and screen for hepatitis B surface antigen, antibodies to hepatitis C virus and antibodies to HIV

7. A urine sample for routine urinalysis, drugs of abuse screen, and pregnancy test (for females only)

8. Questions about alcohol, nicotine and caffeine consumption.

6.2.1 Follow-up procedures

A post-study medical examination will be performed approximately 6 days after the last PK sampling of period 2 has been taken. The examination will be similar to the one performed at screening and will include a complete physical examination, measurement of weight, vital signs, recording a 12-lead standard ECG, blood sample for clinical chemistry and haematology, a urine sample for urinalysis and pregnancy test for females, and assessment of any AEs or required medication.

6.3 Safety

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

6.3.1 Definition of adverse events

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

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

6.3.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, enrolment, treatment, wash-out, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- 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
- Cancer
- Overdose (defined as the accidental or intentional ingestion of any dose of the investigational product that is considered both excessive and medically important).

For further guidance on the definition of a Serious Adverse Event (SAE), see Appendix B to the Clinical Study Protocol.

6.3.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from the time of obtaining informed consent throughout the treatment periods and including the follow-up period. Before the intake of first dose of study drug only SAEs will be recorded.

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 collected for each AE;

- AE (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 Investigational Product (yes or no)
- AE caused healthy volunteer's withdrawal from study *(*yes or no)
- outcome (yes or no).

Additional variables will be collected for all SAEs including treatment given for the event.

The following intensity ratings will be used:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)
4. 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 6.3.2. 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 a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

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 Clinical Study Protocol.

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 laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and other safety variables should only be reported as AEs if they are clinically significant, fulfil any of the SAE criteria, are the reason for discontinuation or interruption of treatment with the *investigational product*, or require the patient to receive specific corrective therapy.

If deterioration in a 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.

6.3.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational 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 study monitor within one day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated study monitor works with the investigator to ensure that all the necessary information is provided to Bristol-Myers Squibb Global Pharmacovigilance and Epidemiology within **one 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform the study monitor of any follow-up information on a previously reported SAE within one 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 all relevant CRF modules) is sent by e-mail or fax to Bristol-Myers Squibb Global Pharmacovigilance and Epidemiology.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.3.5 Laboratory safety assessment

The respective laboratory reference ranges will be provided by the local laboratory and filed in the Investigator Site File.

Each parameter outside the normal range will be assigned as high or low. The investigator has to interpret each "outside the normal range" value as not clinically significant or clinically significant. In the latter case the Investigator has to give a comment and the deviation is judged as an AE.

These laboratory tests will be performed at the , using validated standard methods according to the applicable laboratory standard operating procedure (SOP). Laboratory data will be transmitted electronically from the , to the study site.

For evaluation of haematology, blood (2.7 mL) will be collected into polypropylene tubes containing 15% potassium-Ethylenediaminetetraacetic acid (Monovette 05.1167, Sarstedt).

For evaluation of clinical chemistry, blood (7.5 mL) will be collected into silicone-free polypropylene serum gel tubes (Monovette 01.1602, Sarstedt).

For infectious serology parameters, a blood sample (2.6 mL) will be taken into a serum tube (Monovette 04.1905.001, Sarstedt).

Urinalysis will be performed at the internal laboratory of according to the applicable SOP.

The following laboratory variables will be measured:

Clinical Chemistry	**Haematology**
Serum (S-)Albumin	Blood (B)-Haemoglobin
S-Alanine aminotransferase (ALT)	B-Leukocyte (part.conc)
S- Aspartate aminotransferase (AST)	B-Absolute leukocyte differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes
S-Alkaline phosphatase (ALP)	B-Platelet count
S-Bilirubin, total	
S-Creatinine	**Urinalysis**
S- Glucose	Urine (U)-Glucose (dipstick)
S-Potassium	U-Haemoglobin (dipstick)
S-Sodium	U-Protein (dipstick)
S-Chloride	U-Creatinine
S-Creatinine kinase (CK)	
S-Total protein	**Other samples**
S-Uric acid	S-U-Pregnancy test (females only) (S-βhCG)
	S-Follicle stimulation hormone (FSH) (females only and only at enrolment)

Additionally, at screening all healthy volunteers will be tested for HIV, hepatitis B surface antigen and antibodies to hepatitis C. Urine will be tested for the following drugs of abuse at screening and admission: amphetamines, barbiturates, benzodiazepam, cocaine, methadone, methamphetamine, morphine, phencyclidine, tetrahydrocannabinol, opiates. Tricyclic antidepressant will be analysed in serum. At visit 2 and 3 the healthy volunteers will be screened for alcohol. A serum pregnancy test will be performed at visit 1 (enrolment) and on visit 2 and 3. If a healthy volunteer tests positive to any of these screening tests he/she will be excluded from the study.

Serum/plasma samples will be collected to allow for possible post hoc analysis in case of related AEs at time points specified in Table 1.

For blood volume see section 7.1.

6.3.6 Physical examination

The timing of individual examinations is indicated in the Study Plan (Table 1). A complete physical examination will be performed at screening and follow-up and include an assessment of the following: general appearance, skin, head and neck, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, respiratory and neurological systems.

Height will be measured in centimetres and weight in kilograms in underwear. Measurements should be taken without shoes and the same scale used for all measurements. BMI will be calculated from the height and weight.

A medical history will be recorded at the Screening visit only.

6.3.7 Resting ECG

An ECG recording will be performed as described in Table 1 and Table 2.

The ECG will be recorded at a paper speed of 25 mm/s and a standard calibration of 1 mV (= 10 mm) for each lead with a standard digital ECG and a Cardiosoft® (CS) version 6.51 ECG device, manufactured by General Electrics Medical Systems (GEMS, Freiburg, Germany).

The 12-lead ECGs will be recorded after the healthy volunteers have rested for at least 10 minutes in supine position. Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF), and six pre-cordial leads (V1–V6), according to Wilson, will be used.

Each ECG will include the following information: identification of each lead, study number, subject number, paper speed, voltage calibration as well as date and time of the recording. After conduction, the ECGs will be stored electronically in the CS database and the parameters may be exported to other databases.

The parameters HR, RR, PQ, QRS, QT and QTcB calculated by the Bazett formula (QTc= QT/RR0.5) will be assessed. ECG recordings will capture at least four QRS complexes, i.e. three evaluable RR intervals. All ECG data are captured and assessed electronically.

The investigator or a designate will evaluate whether the ECG is normal or abnormal and whether it is clinically significant, if abnormal.

ECGs may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected by the Investigator for safety reasons. Clinically relevant abnormal findings will be reported as adverse events.

6.3.8 Vital signs

6.3.8.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured using an oscillometric BP rate monitor (Dynamap Pro Care®), manufactured by General Electrics Medical Systems (GEMS) after 10 minutes rest on a bed. Pulse will be recorded simultaneously with the BP measurements by the same monitor. For timings of assessments refer to the Study Plans Table 1 and Table 2.

6.3.8.2 Body temperature

Oral body temperature will be measured for at least one minute using a digital thermometer (DIGItemp®, LDM Pharma, Wesel, Germany) at the times indicated in the Study Plans Table 1 and Table 2.

6.3.9 Other safety assessments

No further safety assessments will be performed.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples for determination of dapagliflozin (4 mL) and metformin (2 mL) in plasma will be taken at the times presented in the study plan Table 2.

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

For blood volume see section 7.1.

6.4.2 Determination of drug concentration

Samples for determination of concentration of dapagliflozin in plasma will be analysed using appropriate bioanalytical methods on behalf of Clinical Pharmacology & DMPK, AstraZeneca, Mölndal, by Atlanbio, France. Full details of the analytical methods used will be described in a separate bioanalytical report. Samples for determination of concentration of metformin in plasma will be analysed using appropriate bioanalytical methods on behalf of Clinical Pharmacology & DMPK , AstraZeneca, Mölndal, Sweden, by Atlanbio. Full details of the analytical methods used will be described in a separate bioanalytical report.

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 4 Volume of blood to be drawn from each healthy volunteer

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	7.5	6	30.0
	Haematology	2.7	6	16.2
	Serology	2.6	1	2.6
	Tricyclic antidepressants	1.1	3	3.3
Pharmacokinetic		6.0	42	252

Table 4 Volume of blood to be drawn from each healthy volunteer

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	7.5	6	30.0
	Haematology	2.7	6	16.2
	Serology	2.6	1	2.6
	Tricyclic antidepressants	1.1	3	3.3
Total				**303.1**

Pregnancy and follicle stimulating hormone will be determined within the sample for clinical chemistry.

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 become available. However, the maximum volume to be drawn from each healthy volunteer will not exceed 450 mL, ie, the same volume as would be drawn during a regular blood donation.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

7.2.1 Pharmacokinetic and safety samples

Samples will be disposed of after the clinical study report has been finalised.

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be disposed of after analysis.

7.3 Labelling and shipment of biohazard samples

The Principal 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 principal investigator keeps full tractability of collected biological samples from the subjects while in storage at the centre until shipment and keeps documentation of receipt of arrival. The sample receiver keeps full tractability of the samples while in storage and during use until used or

disposed. AstraZeneca or representative keeps oversight of the entire life cycle through internal procedures, monitoring of study sites until samples are used/disposed or transferred for long-term storage, while AstraZeneca performs auditing as applicable of external laboratory providers. Samples retained for further use is registered in AstraZeneca bio bank 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 Principal Investigator:

- Ensures healthy volunteers' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.
- Ensures that biological samples from that healthy volunteer, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.
- Ensures 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.
- Ensures 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 on Harmonisation (ICH)/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The Informed Consent Form 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 should approve the final study protocol, including the final version of the Informed Consent Form 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 Ethics Committee, and to the study site staff.

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

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

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

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

Before enrolment of any healthy volunteer into the study, the final study protocol, including the final version of the Informed Consent Form, 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, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, , including Suspected Unexpected Serious Adverse Reactions, where relevant.

8.4 Informed consent

The Principal Investigator 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 that two Informed Consent Forms are signed and one is stored in the Investigator's Study File.

- Ensure a signed Informed Consent Form of the signed Informed Consent Form 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 informed consent form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator 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 Clinical Study Protocol).

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

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

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee 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, Good Clinical

Practice (GCP), guidelines of the ICH, 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 BY 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 Clinical Study Agreement 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 Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and ClinBase™ system utilised.

The Principal Investigator 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 Principal Investigator 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 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 investigational product 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 healthy volunteer (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 healthy 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

Source for all data will be presented in a separate Source Data Document, which will be approved and signed by the Principal Investigator before study start.

Electronic CRF (eCRF), EDC application, medical journal and study specific source documents will act as the source data for all information in the study.

9.4 Study agreements

The Principal Investigator should comply with all the terms, conditions, and obligations of the Project Agreement or equivalent for this study. In the event of any inconsistency between this Clinical Study Protocol and the Project Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of healthy volunteers. In all other respects, not relating to study conduct or treatment of healthy volunteers, the terms of the Project Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or healthy volunteers are enrolled.

9.4.1 Archiving of study documents

Study documents will be archived in the Study Master File (SMF) and the Investigator's Study File.

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 and end in Quarter I/2010.

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 the IPs.

The study will be stopped prematurely if:

- Five or more subjects have adverse events of similar type and of moderate or greater severity not previously reported in ≥2% of subjects in Phase 3 clinical trials. Degree of severity will be defined by CTC criteria.
- One serious life threatening adverse event occurs in a cohort that is highly likely to be related to the IMP and unrelated to its mechanism of action.
- Four or more subjects show an unexplained increase in liver enzymes (ALT/AST) ≥3 times upper limit of normal in two consecutive samples.
- Data not known before become available and raise concern about the safety of the study drug so that continuation would pose potential risk to the subjects.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

10.1 Data collection methods and data validation at study site

10.1.1 Data flow

ClinBase™ system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and study management. All clinical and laboratory data, except those which are paper based, will be collected by the eSource system ClinBase™. Only paper-based data will be subject to data entry. For electronic data, no data entry will be performed. Data entered on pCRF should be recorded legibly in blue or black ballpoint pen. Correction fluid or covering labels must not be used.

The responsible monitor will check data at the monitoring visits to the study site. The Investigator will ensure that the data collected are accurate, complete and legible. Data will be validated within ClinBase™ by the Investigator and the study monitor before being exported. Any changes made during validation will be documented with a full audit trail within ClinBase™.

designs and builds a database in iVal* to enter the paper-based data for adverse event and concomitant medication. The database and entry screens will be built and validated following a formal, documented verification plan and the system will be tested against the specification for the entry system. The setup will be controlled by test data entry. A standardised setup of Statistical Analysis System (SAS®) data sets in AstraZeneca specification will be done by the SAS® clinical data programmer. Verification of the setup will be performed with dummy and test data.

*The iVal system is a 21 CFR part 11 compliant application ensuring high data quality. The iVal system is a clinical database management system composed of several modules including, but not limited to, a set-up tool, a database designer (data dictionary editor), an entry screen designer (data entry manager), a query manager (iQue), a validation-programming environment, and a SASTM dataset export module (iSAS). For more information refer to the Data Management Plan.

The clinical data manager will develop a data verification specification (DVS) according to the protocol, the data dictionary of the iVal database for paper based-data and the description of the SAS® table set for electronic data. Computerised checks to be performed on the data imported or entered into the databases will be defined in this document. The DVS will be sent to AstraZeneca or representative for review and approval.

Paper-based data will be sent to data management and entered into iVal. These data will be exported via the module iSAS later on and merged with the SAS® tables in AstraZeneca format. The SAS® data sets will be used for verification of the electronic study data following the specifications listed in the DVS. Only trained staff will have access to the databases. Every change will be fully audit-trailed.

The ClinBase™ data files will be imported into SAS® data sets and the imported data checked by the related verification programmes specified in the DVS. Data will be changed only in a controlled, audit-trailed, environment. After these data are considered as clean, they will be mapped into AstraZeneca data structure.

All study related electronic source data captured in ClinBase™ will be transferred from ClinBase™ via ClinResult to Data Management after monitoring. These data will be imported into the SAS® data sets. Paper based data will be sent to Data Management after they have been monitored. Data Management reviews, logs and files them.

External PK concentration data will be transferred to Data Management as specified by a Bio analytical data transfer specification. This data will be reconciled against the source ClinBase™ database and any discrepancies will be communicated to the Bio analytical Laboratory.

Any missing, implausible or inconsistent recordings will be referred back to the Investigator using a data query form and be documented for each individual healthy volunteer before clean file status is declared.

The following data will be captured as source electronically using ClinBase™:

- Dates and times of all blood and urine samples
- Dates and time of all dosing
- Pulse and BP
- Safety laboratory data

- ECG
- Height
- Weight

10.1.2 Study Data Management Plan (DMP)

The Study Data Management Plan (DMP) will describe the methods used to collect, check and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process. Further the DMP will also describe the data flow and timelines within the study.

10.1.3 Coding tools and dictionaries

Adverse events and diagnoses from medical history will be classified according to the terminology of Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be classified according to the WHO Drug Dictionary. All coding will be performed by

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of safety variables

The closest observation prior to first administration of investigational product will be regarded as baseline.

Change from baseline variables will be calculated as the value minus the value at baseline.

11.1.1 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 Investigational Product due to Adverse Events (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory and/vital signs 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.

11.2 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic (PK) analyses of the plasma concentration data for dapagliflozin and metformin will be performed by Derivation of PK parameters will be preformed

using the WinNonlin's standard non-compartmental approach (WinNonLin version 5.01, WinNonLin, Pharsight, Mountain View, CA, USA).

The actual sampling times will be used in the PK parameter calculations. Plasma concentrations below limit of quantification (LOQ) will be excluded from the calculations except at time points prior to C_{max}, where plasma concentrations below LOQ will be taken as zero at protocol time zero and as missing at all other time points in the calculation.

The primary objectives of the study are to determine AUC_{0-t}, AUC_{inf} and C_{max} for dapagliflozin and metformin as single doses and within each FDC formulation and the and bioequivalence will be tested with respect to these two PK parameters for

> **Part I:** one 2.5 mg/850 mg FDC tablet and one single dose of 2.5 mg dapagliflozin together with one single dose of 850 mg metformin

and

> **Part II**: one 5 mg/1000 mg FDC tablet and one single dose of 5 mg dapagliflozin together with one single dose of 1000 mg metformin

all administered in the fed state.

The following PK parameters will be determined:

- $AUC_{(0-t)}$ Area under plasma concentration-time curve from zero to time t [amount•time/volume]
- AUC_{inf} Area under plasma concentration-time curve from zero to infinity [amount•time/volume]
- C_{max} Maximum plasma (peak) drug concentration [amount/volume]
- t_{max} The time relative to administration to reach C_{max}, [h]
- $t_{1/2}$ The terminal phase half-life calculated as $\ln(2)/\lambda_z$, [h^{-1}]

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

12.1 Description of analysis sets

12.1.1 Pharmacokinetic analysis set

The PK analysis will be performed using the PK analysis set including all subjects who received the investigational product and who have evaluable PK data appropriate for the

comparison of interest (with no major protocol deviations or violations thought to significantly affect the pharmacokinetics of the drug).

12.1.2 Safety analysis set

The safety population is defined as all subjects who receive at least one dose of IP and for whom any post-dose data are available. The safety population will be used for the analysis of all safety variables and the analysis will be done according to actual treatment received, regardless of randomisation. Post-dose data imply that there was a contact during which an opportunity was given to report any health problems.

12.2 Methods of statistical analyses

12.2.1 General principles

The PK analysis will be performed using the PK analysis set including all subjects who received the investigational product and who have evaluable PK data appropriate for the comparison of interest (with no major protocol deviations or violations thought to significantly affect the pharmacokinetics of the drug).

12.2.2 Subject characteristics

Continuous variables will be summarised using descriptive statistics (n, mean, standard deviation [SD], min, median, max). Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment.

12.2.3 Pharmacokinetics

The primary objectives of this study are to demonstrate bioequivalence for newly formulated FDC tablets versus the individual dapagliflozin and metformin IR tablets (free combination) of dapagliflozin/metformin 2.5 mg/850 mg and for 5 mg/1000 mg. For both objectives, bioequivalence will be demonstrated if the 90% confidence interval (CI) for the formulation effect is contained within the interval of 0.8000-1.2500 for $AUC_{(0-t),}$ AUC_{inf} and C_{max} with respect to both dapagliflozin and metformin.

The study has two parts: Part I is 2-treatment, 2-period, crossover design to evaluate bioequivalence for the 2.5 mg/850 mg formulation and Part II is a 2-treatment, 2-period, crossover design to evaluate bioequivalence for the 5 mg/1000 mg formulation. In Part I, subjects will be randomized to one of two sequences in a 1:1 allocation. Sequence 1 will administer the FDC in period 1 and the free combination in period 2. Sequence 2 will administer the treatments in the reverse order. For Part II, subjects will be randomized in the same way as in Part I.

$AUC_{(0-t)}$, AUC_{inf} and C_{max} will be log-transformed prior to analysis. All endpoints will be analyzed using an analysis of variance (ANOVA) model for each part separately, with sequence, period and formulation as fixed effects and subject within sequence as a random effect. The results of the analysis will be presented in terms of the estimated geometric mean for each formulation with corresponding 95% confidence interval, and the estimated

formulation effect (ratio of geometric means) with a 90% confidence interval. Geometric means will be estimated by back-transformation of least squares means from the log-transformed data with adjustment for any imbalances in the design. All other pharmacokinetic parameters will be summarized by formulation using descriptive statistics only.

Graphical presentations will be used as appropriate. Examples may include line graphs showing individual or mean development over time.

12.2.4 Safety and tolerability

Continuous variables will be summarised using descriptive statistics (n, mean, SD, min, median, max) by treatment group. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment group. Graphical presentations will be used as appropriate. Examples include shift plots showing pre-treatment values on the horizontal axis and post-treatment values on the vertical axis.

12.2.4.1 Adverse events

Adverse events will be summarised by preferred term and system organ class using MedDRA vocabulary. Furthermore, listings of serious adverse events and adverse events that led to withdrawal will be made and the number of subjects who had any AEs, SAEs, AEs that led to withdrawal, and adverse events with severe intensity will be summarised. AEs that occur before dosing will be reported separately.

12.2.4.2 ECG

ECG results will summarized in a frequency table displaying number of subjects with a normal/abnormal assessment. Individual subject data will be provided in a listing.

12.2.4.3 Laboratory variables

Clinical chemistry, haematology and urinalysis variables will be described by shift plots, descriptive statistics, subject listings and frequency tables of values outside project specific reference ranges, details of which will be presented in a separate comprehensive SAP.

12.2.4.4 Vital Signs

Summary statistics for all vital signs data will be presented and will include mean, standard deviation, min, max, details of which will be presented in a separate comprehensive SAP.

12.3 Determination of sample size

To determine the sample size for this study, initial estimates of formulation effect (geometric mean ratio) were obtained from Bristol-Myers Squibb Study MB102026 which examined a different FDC of dapagliflozin and metformin. Estimates of the intra-subject variability (MSE) for dapagliflozin $AUC_{(0-t)}$ and metformin C_{max} and $AUC_{(0-t)}$ were also obtained from this study, whereas the estimate for dapagliflozin C_{max} was obtained from Bristol-Myers Squibb Study MB102005 (the median estimate from dapagliflozin studies MB102005, MB102019 and MB102026). From these sources, data for initial estimates of formulation

effect and assumed intra-subject variability (MSE of log-transformed data) were 0.932 (0.041), 1.005 (0.009), 0.953 (0.025), and 1.001 (0.012), for dapagliflozin C_{max} and $AUC_{(0-t)}$, and metformin C_{max} and $AUC_{(0-t)}$, respectively.

If the ratio of true geometric means is actually 0.90 for dapagliflozin C_{max}, 1.00 for dapagliflozin $AUC_{(0-t)}$, 0.95 for metformin C_{max}, and 1.00 for metformin $AUC_{(0-t)}$, then with 54 evaluable subjects in Part I, there is 90% power to establish bioequivalence with respect to dapagliflozin C_{max} and >99% power for each of the remaining 5 measures (assuming same results for AUC_{inf} as for $AUC_{(0-t)}$). With 6 subjects anticipated not to complete both periods of the study, a total of 60 subjects are needed in each Part.

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 6.3.4.**

In the case of a medical emergency the investigator may contact the Study Team Physician and the Medical Science Lead at AstraZeneca. If the Study Team Physician is not available, contact the Senior Project Manager at

Name	Role in the study	Address & telephone number
Medical Science Director	SDT Physician responsible	
Medical Science Lead	Medical Science Lead Clinical Pharmacology EPMT	
	Study physician	

Name	Role in the study	Address & telephone number
	Senior Project Manager at	

13.2 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. **All occurrences of overdose must be reported as an SAE (see section 6.3.2).** If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed.

13.3 Pregnancy

If a patient becomes pregnant, the investigational product should be stopped 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 Bristol-Myers Squibb using the same procedure as for SAE reporting (6.3.2). 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 investigational product under study may have interfered with the effectiveness of a contraceptive medication.

However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

14. LIST OF REFERENCES

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Matthei et al 2000
Matthaei S, Stumvoll M, Kellerer M, Haring HU. Pathophysiology and Pharmacological treatment of insulin resistance. Endocr Rev 2000;21:585–618.

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UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837–53.

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Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G. ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006 Dec 7; 355(23):2427-43. Epub 2006 Dec 4. Erratum in: N Engl J Med. 2007 Mar 29;356(13):1387-8.

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A two part, open label, randomized, single-centre, phase I bioequivalence study comparing (Part I) the fixed dose combination 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 fixed dose combination 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

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.
I agree to the terms of this study protocol

AstraZeneca Research and Development
site representative

ASTRAZENECA SIGNATURE(S)

A two part, open label, randomized, single-centre, phase I bioequivalence study comparing (Part I) the fixed dose combination 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 fixed dose combination 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

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol

AstraZeneca Research and
Development site representative

ASTRAZENECA SIGNATURE(S)

A two part, open label, randomized, single-centre, phase I bioequivalence study comparing (Part I) the fixed dose combination 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 fixed dose combination 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

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This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol

Projectmanagement

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A two part, open label, randomized, single-centre, phase I bioequivalence study comparing (Part I) the fixed dose combination 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 fixed dose combination 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

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This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review. I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators

Centre No.: 1

Signature:

Clinical Study Protocol Appendix B

Drug Substance	Dapagliflozin
Study Code	D1691C00002
Edition Number	1.0

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	Dapagliflozin
Study Code	D1691C00002
Edition Number	1.0

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.