Clinical Study Protocol

Drug Substance	Dapagliflozin
Study Code	D1692C00002
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Date	

An Open-label, Multi-centre, Drug-drug Interaction Study to assess the effect of Voglibose (0.2 mg tid) on the Pharmacokinetics, Safety and Tolerability of single oral administration of dapagliflozin (10 mg) in Japanese Patients with Type 2 Diabetes

Sponsor:

AstraZeneca K.K.
Bristol-Myers K.K.

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

PROTOCOL SYNOPSIS

An Open-label, Multi-centre, Drug-drug Interaction Study to assess the effect of Voglibose (0.2 mg tid) on the Pharmacokinetics, Safety and Tolerability of single oral administration of dapagliflozin (10 mg) in Japanese Patients with Type 2 Diabetes

Principal Investigator

The names of the investigators are described in Supplement A, "Investigations and Study Administrative Structure".

Study centre(s) and number of subjects planned

Study Centres: 2 centres are planned for participation

Number of Subjects: 22 randomised Japanese subjects

Study period		Phase of development
Estimated date of first subject enrolled	January 2010	Phase 1
Estimated date of last subject completed	April 2010	

Objectives

Primary objective

- To evaluate the pharmacokinetics of dapagliflozin when administered alone or in combination with voglibose in Japanese patients with type 2 diabetes by assessment of AUC and C_{max} of dapagliflozin.

Secondary objectives

- To evaluate the safety and tolerability of dapagliflozin when administered alone or in combination with voglibose in Japanese patients with type 2 diabetes.
- To evaluate the pharmacokinetics of dapagliflozin when administered alone or in combination with voglibose in Japanese patients with type 2 diabetes by assessment of AUC_{0-t}, t_{max}, $t_{1/2}$, CL/F.

Study design

This is an open-label, multi-centre drug-drug interaction study to assess the effect of voglibose 0.2 mg tid on the pharmacokinetics, safety and tolerability of dapagliflozin when a single oral

dose of dapagliflozin 10 mg is administered in Japanese patients with type 2 diabetes treated with voglibose. The dose of volibose has to be stable for at least 2 months, but one change in voglibose dose to 0.2 mg tid by 4 weeks before enrolment is allowed.

In this study 22 Japanese patients with type 2 diabetes will be assigned to treatment. Each patient will take a single oral dose of 10 mg dapagliflozin (Visit 2) with voglibose and plasma samples will be collected through Visit 4 (up to 72 hours=3 days after dose) for pharmacokinetic assessment. After a wash-out period (7[+7] days) following the 1st pharmacokinetic sampling period (PK sampling period I), a single oral dose of 10 mg dapagliflozin will be administered without voglibose. Plasma samples will be collected through Visit 7 (up to 72 hours=3 days after dose) for pharmacokinetic assessment (PK sampling period II).

The patients will take voglibose just before each meal (tid) until Visit 4. From the start of the wash-out period (Study Day 4) until the last day of blood sampling for pharmacokinetic assessment (Visit 7), the patients will stop taking voglibose.

Target subject population

Male or female patients with type 2 diabetes aged 20 or older

Investigational product, dosage and mode of administration

Dapagliflozin 10mg tablets. Tablets will be administered orally, as a single dose in the morning during fasting conditions.

Comparator, dosage and mode of administration

Not applicable.

Duration of treatment

Each patient will receive a single oral dose of dapagliflozin 10 mg twice, one on the 1st day of the pharmacokinetic (PK) sampling period I (with voglibose) and one on the 1st day of the PK sampling period II (dapagliflozin alone). The PK sampling periods will be separated by a wash-out period of 7 (+7) days between the last dose of voglibose in period I and the dose of dapagliflozin in period II.

Outcome variable(s):

Primary outcome variables

- AUC and C_{max} of dapagliflozin

Secondary outcome variables

- AEs, laboratory values, electrocardiogram, pulse, blood pressure and physical examination findings.$AUC_{0\text{-}t}$, t_{max}, $t_{1/2}$, CL/F of dapagliflozin.

Statistical methods

All PK and safety data will be summarised by dosing condition using descriptive statistics.

The pharmacokinetic variables AUC and C_{max} will be log-transformed before analysis. They will be analysed using a mixed model ANOVA with fixed effects for the dosing condition (with voglibose or without voglibose) and a random effect for patients. Estimates and confidence intervals of the difference between the dosing conditions will first be constructed in the log scale. Then the estimates and confidence intervals of ratio of geometric means between the dosing conditions in the original scale will be obtained by taking anti-logarithms. The estimates and 2-sided 90% confidence intervals of the ratio of geometric means will be presented for:

- AUC (with voglibose) /AUC (without voglibose)
- C_{max} (with voglibose) / C_{max} (without voglibose)

It will be concluded that there is no pharmacokinetic drug-drug interaction if the confidence interval falls within 80% - 125% for AUC and C_{max} of dapagliflozin.

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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 6.4.1)
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AP (ALP)	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{(0-t)}$	Area under plasma concentration versus time curve from zero to the last quantifiable concentration
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CK	Creatine kinase
CL/F	Oral plasma clearance
C_{max}	Maximum plasma (peak) concentration
CRF	Case Report Form (electronic/paper)
DAE	Discontinuation of Investigational Product due to Adverse Event
ECG	Electrocardiogram
FPG	Fasting plasma glucose
FSH	Follicle simulating hormone
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin, Hemoglobin A1c
HCG	Human chorionic gonadotropin
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification

Abbreviation or special term	Explanation
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
PK	Pharmacokinetic
SAE	Serious adverse event (see definition in Section 6.4.2).
SCr	Serum Creatinine
SD	Standard deviation
TB	Total bilirubin
tid	ter in die (three times a day)
t_{max}	Time to maximum concentration
TSH	Thyroid Stimulating Hormone
$t_{1/2}$	Terminal half-life
T2DM	Type 2 diabetes mellitus
ULN	Upper limit normal
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Recent estimates indicate that there were 150 million people in the world with type 2 diabetes mellitus (T2DM) at the beginning of the new millennium. It is believed that this number will double in the next 25 years. In Japan, diabetes mellitus patients and impaired glucose tolerance (IGT) is estimated as 8.9 million and 13.2 million, respectively, and in total, 22 million (The Summary of the National Health and Nutrition Survey 2007). The number of death caused by diabetes mellitus during 2007 was reported as 14,000 (Vital Statistics, 2007).

T2DM is characterized by beta-cell dysfunction and peripheral insulin resistance leading to hyperglycaemia(Matthaei et al 2000, Meier and Butler 2005). Chronic hyperglycaemia has been associated with the development of both macrovascular (myocardial infarction, stroke), and microvascular (nephropathy, retinopathy) complications (UKPDS Group 1998a). Every year, 3,500 people suffer from loss of eyesight caused by diabetic retinopathy (The 2005 Data on Diabetic Retinopathy by the Japan Ophthalmologists Association). The primary disease that most often led to initiation of dialysis was diabetic nephropathy that led to initiation of dialysis, with 15,750 patients (43% of total) (An Overview of regular dialysis treatment in Japan (as of December 31, 2007)).

Current treatment regimens aiming to reduce glucose levels in T2DM patients are categorized into 6 types, which have focussed on the stimulation of insulin secretion (e.g., sulfonylureas (SUs), rapid-acting insulin secretion stimulators (glinides)), the reduction of peripheral insulin resistance (e.g., biguanides (BGs), thiazolidine derivatives (TZDs)), the inhibition of intestinal glucose absorption(e.g. α-glucosidase inhibitors (AGIs)), or the addition of exogenous insulin. However, the limited efficacy as well as the induction of side effects (e.g., hypoglycaemia, oedema, weight gain, etc.) clearly underlines the need for novel antidiabetic treatment strategies with a new mechanism of action and more favourable risk/benefit profile.

Intestinal absorption and renal re-absorption of glucose are mediated through sodium-glucose transporters (Silverman 1991). Two sodium-dependent glucose transporters, SGLT1 and SGLT2, have been identified as the major transporters of glucose in the human (Wright 2001, Thomson and Wild 1997). SGLT1 is expressed in the gastrointestinal tract, heart, skeletal muscle, liver, lung, and kidney, while SGLT2 is expressed almost exclusively in the kidney. SGLT2 expression is localized to the S1 segment of the proximal tubule, where > 90% of renal glucose reabsorption occurs (Deetjen P et al 1992). Human mutations in SGLT2 are associated with familial renal glucosuria. These patients present with glucosuria secondary to a decrease in glucose reabsorption in the proximal tubule. They have normal plasma glucose levels. From the information available, these patients have normal life-span and no abnormalities other than the increase urinary glucose excretion (Santer et al 2003, van den Heuvel et al 2002). Thus SGLT2 appears to be the major transporter responsible for renal glucose transport, mediating glucose re-uptake from the glomerular filtrate. Inhibition of SGLT2 therefore provides a promising novel treatment strategy to reduce high blood glucose levels via enhanced renal glucose excretion.

Dapagliflozin has been designed as a potent and selective inhibitor of the renal sodium-glucose transporter, SGLT2. This compound is being developed as an orally-active agent for the treatment of T2DM. Since this compound has the new mechanism of action, ie, induction of glucose excretion into urine independent of insulin action, it is expected to represent a novel therapeutic approach for the treatment of this disorder.

1.2 Research hypothesis

The hypothesis tested in this study is that voglibose will have no effect on the pharmacokinetics of dapagliflozin (10 mg) in Japanese patients with type 2 diabetes (T2DM). In addition, the safety and tolerability in this combination therapy will be evaluated as the secondary objectives.

1.3 Rationale for conducting this study

There is an unmet need in the treatment of diabetes mellitus. With the current medical therapy less than 50% of patients with diabetes reach glycemic control goals (UKPDS Group 1998a, UKPDS Group 1998b). Therefore, the development of medications with new mechanisms of action for the treatment of diabetes is desirable. Dapagliflozin, with its novel mechanism of action, inhibits SGLT2 and may result in lowering of plasma glucose regardless of the patient's insulin sensitivity and beta-cell functional secretory status.

In the global single ascending dose Phase 1 study in healthy volunteers (MB102001), there was a dose-dependent increase in urinary glucose excretion from 2.5 to 20 mg. Doses higher than 20 mg (50 to 500 mg) did not cause greater urinary glucose excretion than the 20 mg dose.

In the global multiple ascending dose Phase 1 study in healthy volunteers (MB102002), there was a dose-dependent increase in urinary glucose excretion from 2.5 mg to 20 mg/day. The urinary glucose excretion was similar for subjects taking 20 mg/day and 50 mg/day. It appears that in healthy subjects the peak effect in urinary glucose excretion is seen at 20 mg/day.

In the global Phase 2b study (MB102008), dose range from 2.5 to 50 mg was administered once daily oral ingestion over 12 weeks in patients with T2DM. A statistically significant reduction in HbA1c from baseline to Week 12 was achieved in all dapagliflozin groups compared with placebo ($p < 0.008$ or less for each dose group), but was not demonstrated to be dose dependent within the study dose range. In the global phase 2b study, dapagliflozin was demonstrated to be well-tolerated in subjects with T2DM.

In the Japan single ascending dose Phase 1 study (MB102010), dapagliflozin 2.5 mg, 10 mg, 20 mg and 50 mg was administrated to healthy volunteers. Preliminary data show that after single oral dose of dapagliflozin, urinary glucose excretion increased in proportion to dose while urinary glucose excretion remained constant following single oral dose of matching placebo.

In the Japan multiple ascending dose Phase 1 study (MB102025), multiple oral doses of dapagliflozin 2.5 mg, 10 mg and 20 mg for 14 days were generally safe and well tolerated in

Japanese T2DM subjects. Preliminary data show that administering with dapagliflozin increased the amount of glucose excreted in urine almost dose-dependently and slightly increased the amount of calcium excreted in urine.

In addition the Phase 2 study to evaluate the effect of dapagliflozin doses from 1 to 10 mg daily for 12 weeks is ongoing.

Voglibose is an oral antihyperglycaemic agent of α-glucosidase inhibitors (α-GI), widely used in the management of type 2 diabetes in Japan. It is not absorbed into circulation and works exclusively inside of gastrointestinal truct. α-glucosidase inhibitors have a different mechanism of action from that of dapagliflozin, and suppress postprandial hyperglycemia by interfering with disaccharidase (α-glucosidase) in the mucosa of the small intestine, that works in the final stage of carbohydrate digestion, thus delaying glucose digestion and absorption.

Dapagliflozin and voglibose are intended to be used in combination in the future. This justifies assessing the effect of voglibose on the pharmacokinetics, safety and tolerability of dapagliflozin when administering dapagliflozin to Japanese patients with type 2 diabetes treated with voglibose. Combination therapy with multiple antidiabetic drugs is also commonly done in Japanese medical practice as well and the one including α-glucosidase inhibitors is the case. Voglibose is selected as the most widely used α-glucosidase inhibitor in Japan.

1.4 Benefit/risk and ethical assessment

This study includes an experimental compound, dapagliflozin, being developed as a potential new therapy for hyperglycemia in subjects with T2DM. In the Japan Phase 1 study and the global Phase 1, 2a and 2b studies dapagliflozin was generally safe and well tolerated.

In the Japan Phase 1 (MB102025), multiple oral doses of dapagliflozin 2.5 mg, 10 mg and 20 mg for 14 days were generally safe and well tolerated in Japanese T2DM subjects. There were no deaths, serious adverse events (SAEs) or adverse events (AEs) leading to discontinuation of investigational product in this study. Fourteen (14) of 27 subjects experienced 19 AEs following administration of dapagliflozin, and 2 of 9 subjects experienced 3 AEs following the dose of placebo.

The Japan Phase 2b (D1692C00005) is now ongoing. Subjects with T2DM receive 1 to 10mg of dapagliflozin or placebo.

In the global Phase 2a study (MB102003), in which subjects received dapagliflozin (up to 100 mg daily), placebo or metformin daily for 2 weeks, gastrointestinal(GI) events were the most commonly reported AEs. No SAE was reported during the double-blind period.

In the global Phase 2b study (MB102008), subjects with T2DM received dapagliflozin (up to 50 mg daily), placebo, or metformin, for 12 weeks. Subjects receiving dapagliflozin, in comparison to placebo, exhibited declines in HbA1c and dose-related decreases in fasting plasma glucose (FPG). In addition, subjects with dapagliflozin therapy exhibited decreases in

body weight over the 12-week treatment period when compared to baseline weight as well as when compared to placebo. SAEs were reported in 4 subjects in the dapagliflozin-treatment groups, which were considered by the investigators not related to study medication. There were no deaths reported. Urinary tract infections were more common in dapagliflozin than in placebo but similar to that in the metformin group. Genital tract infections were more frequent in dapagliflozin-treated subjects compared with subjects receiving placebo, especially at the higher dapagliflozin doses of 20 and 50 mg/day. There were no reports of confirmed hypoglycemia, defined as symptoms of hypoglycemia with fingerstick glucose ≤ 50 mg/dL, during the double-blind period. The percentage of subjects with AEs of hypoglycemia was higher in the dapagliflozin treatment groups compared with the placebo group, but similar to that in the metformin treatment group. None of the events of hypoglycemia were assessed by the investigator to be of severe intensity. Dapagliflozin administration was associated with increases in urine production, accompanied by changes in clinical and laboratory data consistent with mild plasma volume reduction. Changes in serum electrolyte concentrations were minor and infrequent.

Previous studies have indicated that dapagliflozin is effective in treatment of T2DM because of its new mechanism of action, ie, ability to reduce high blood glucose level via enhanced renal glucose excretion. However, since patients will receive only two single doses of dapagliflozin in this study, which have no expected effect on glucose or lipid metabolism, there are no direct benefits for the patients participating in this study except a thorough medical examination.

The dose of 10 mg was chosen for this study as the expected highest dose for type 2 diabetes patients since 10 mg is the highest dose in the ongoing Phase 2b study in Japanese patients with type 2 diabetes (D1692C00005) and Phase III studies overseas.

Special consideration will be taken to monitor effects on blood pressure, electrolytes, renal function and liver function. Women of child-bearing potential should not be included unless they are using highly effective methods of contraception during treatment with dapagliflozin.

2. STUDY OBJECTIVES

2.1 Primary objective

- To evaluate the pharmacokinetics of dapagliflozin when administered alone or in combination with voglibose in Japanese patients with type 2 diabetes by assessment of AUC and C_{max} of dapagliflozin.

2.2 Secondary objectives

- To evaluate the safety and tolerability of dapagliflozin when administered alone or in combination with voglibose in Japanese patients with type 2 diabetes.

- To evaluate the pharmacokinetics of dapagliflozin when administered alone or in combination with voglibose in Japanese patients with type 2 diabetes by assessment of AUC_{0-t}, t_{max}, $t_{1/2}$, CL/F.

2.3 Safety objective

See Section 2.1.

2.4 Exploratory objectives –Not applicable

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is an open-label, multi-centre drug-drug interaction study to assess the effect of voglibose 0.2 mg tid on the pharmacokinetics (PK), safety and tolerability of dapagliflozin when a single oral dose of dapagliflozin 10 mg is administered to Japanese patients with type 2 diabetes mellitus (T2DM) treated with voglibose.

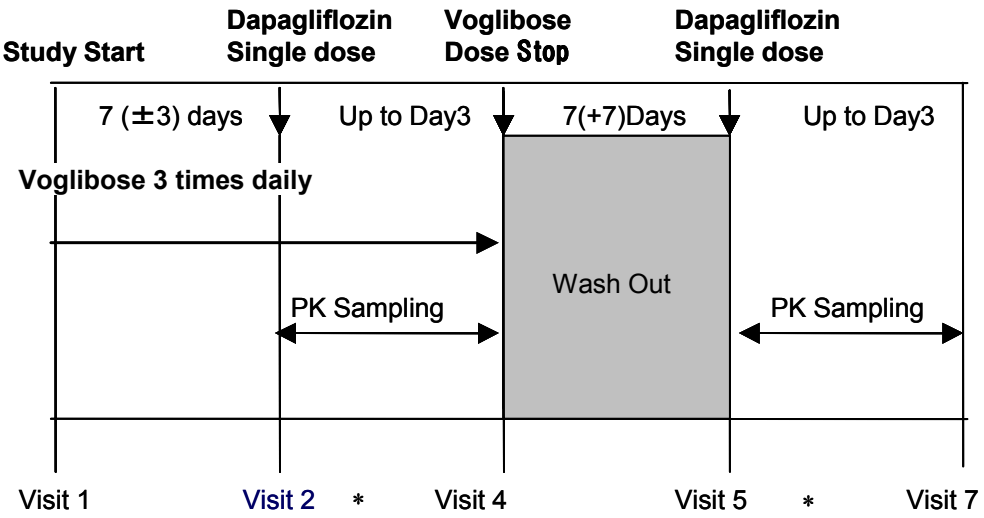
In this study 22 Japanese patients with T2DM will be assigned to treatment. The patients should be on stable treatment with voglibose at least 8 weeks before enrolment (one change in voglibose dose to 0.2 mg tid by 4 weeks before enrolment is allowed).

The study consists of two PK sampling periods: period I of a single dose of dapagliflozin with voglibose and period II of a single dose of dapagliflozin alone. The PK sampling periods will be separated by a wash-out period of 7(+7) days between the last blood sampling in period I and the dose of dapagliflozin in period II.

In period I, each patient will take a single oral dose of 10 mg dapagliflozin (Visit 2) together with voglibose and plasma samples will be collected through Visit 4 (up to 72 hours = 3 days after dose) for PK assessment. In period II, after the wash-out period, a single oral dose of 10 mg dapagliflozin will be administered without voglibose. Plasma samples will be collected through Visit 7 (up to 72 hours = 3 days after dose) for PK assessment.

The patients will take voglibose just before each meal (tid) until and including Study day 3 (Visit 4). The patients will stop taking voglibose on Study day 4 and no voglibose will be taken until after the last blood sampling for PK assessment on Study day 14 (Visit 7).

Figure 1 Study flow chart



* At Visits 2 and 5, patients will arrive at the study site on the day before the day of administration of dapagliflozin and stay at the site until the next day of the day of administration of dapagliflozin.

Table 1 Study plan

	Enrolment	PK sampling period I				Wash-out	PK sampling period II			
Visit number	**V1**	**V2 (hospitalisation)**		**V3**	**V4**		**V5 [a] (hospitalisation)**		**V6**	**V7 follow-up [b]**
Study day (day)	**-7 (±3)**	**0**	**1**	**2**	**3**	**4-10 (+7)**	**11**	**12**	**13**	**14**
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Demography and medical/surgical/diabetes history	X									
Concomitant medication	←	―	―	―	―	―	―	―	―	→
Pregnancy test [c]	X						X			X
Laboratory assessments	X	X	X		X		X	X		X
Urine assessments		X	X		X		X	X		X
Spot urine collection	X									
Hepatitis screening panel	X									
Physical examination		X			X		X			X
dapagliflozin administration		X					X			
Blood sampling for PK analysis [e]		X	X	X	X		X	X	X	X [d]

Table 1 Study plan

	Enrolment	PK sampling period I				Wash-out	PK sampling period II			
Visit number	**V1**	**V2 (hospitalisation)**		**V3**	**V4**		**V5 [a] (hospitalisation)**		**V6**	**V7 follow-up[b]**
Study day (day)	**-7 (±3)**	**0**	**1**	**2**	**3**	**4-10 (+7)**	**11**	**12**	**13**	**14**
12-lead ECG [f]		X								X
Vital signs (pulse, BP) [f]	X	X	X	X	X		X	X	X	X
Weight	X	X		X	X		X		X	X
Height		X								
SAE recording	◄	———	———	———	———	———	———	———	———	►
AE recording	◄	———	———	———	———	———	———	———	———	►
Diet and life-style advice	X									
Drug accountability		X					X			

a If a patient takes any concomitant drugs (except antidiabetic agents and glucocorticoids) during the washout period (Study day 4-10) when medically needed, Visit 5 (2nd dapagliflozin administration) should be conducted ≥7 days after the last dose of the concomitant drugs.
b Follow-up examination for a discontinued patient will be performed at least 3 days after the last administration of dapagliflozin (Visit 2 or 5).
c Pregnancy test will be conducted for pre-menopausal women of child-bearing potential at enrolment, Visit 5 and the last visit. In the event of suspected pregnancy any time during the study, the test should be repeated. If the results are positive, the subject should be withdrawn from the study and AstraZeneca must be notified immediately.
d No blood sampling for PK analysis will be needed at the time of follow-up for the patient who did not complete Visit 5.
e In the PK sampling period I and II, plasma samples will be collected pre-dose of dapagiflozin and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 14, 24, 48 and 72 hour after dose of dapagliflozin.
f ECG and Pulse rate/BP should be measured more than or equal to 10 minutes before blood sampling.

3.2 Rationale for study design, doses and control groups

3.2.1 Choice of outcome variables

Dapagliflozin and voglibose are intended to be used in combination. In order to obtain a more complete and relevant picture of a potential drug-drug interaction, the systemic exposure of dapagliflozin when administered alone or in combination with voglibose, will be evaluated. AUC and C_{max} of dapagliflozin have been chosen as the primary endpoints. Since voglibose is not absorbed from gastrointestinal tract (Hiraga K et al 1992), no blood samples for determination of voglibose plasma concentrations will be collected in this study.

3.2.2 Choice of study period

Owing to the half-life of dapagliflozin ($t_{1/2}$ of healthy subjects in the Japan single ascending dose study (MB102010) was 12.1 hours and the exposure of T2DM patients in the Japan

multiple ascending dose study (MB102025) was 1.5 times higher than healthy subjects) and the possible extension by interaction with voglibose, it is necessary to draw blood samples until 72 hours after dapagliflozin dosing. A wash-out period of 7 (+7) days between PK sampling periods is considered necessary in order for dapagliflozin and voglibose to be eliminated to remove carry-over effect. As study design, only single sequence fashion (combination followed by dapagliflozin mono-therapy) is adopted in terms of operational feasibility since it takes at least 4 weeks for voglibose to stabilize gastrointestinal condition and adverse events.

3.2.3 Choice of study population

FPG and HbA1c

The upper limit for fasting plasma glucose (FPG) and HbA1c at enrolment, FPG ≤180 mg/dL, and HbA1c ≤8.5 % was chosen to select a patient population with diabetes without risking the patient's health due to sustained hyperglycaemia.

Pregnancy or breastfeeding

Dapagliflozin has not been tested in pregnant women and the risks to embryo, foetus, and infant are unknown. For this reason, women who are pregnant or breastfeeding are excluded and women of child-bearing age are instructed to take precautions to avoid becoming pregnant during the study.

Other

The purpose of the majority of the inclusion and exclusion criteria is to limit confounding factors that may complicate the interpretation of the study results or to exclude patients whose safety could be compromised by participation in the study.

3.2.4 Choice of dose

[Dapagliflozin]

In the ongoing dose-finding study in Japanese patients with type 2 diabetes (D1692C00005), the doses, 1, 2.5, 5 and 10 mg were chosen. In the overseas studies, 2.5, 5 and 10 mg are included in the Phase III development programme with double-blind controlled studies with duration of up to 2 years.

The dose of 10 mg was chosen for this study as the expected highest dose for type 2 diabetes patients.

[Voglibose]

The dose of voglibose used in the study, 0.2 mg tid, is a commonly used dose in clinical practice. To allow reliable evaluation of the effect on the pharmacokinetics of dapagliflozin, it is important that the patients are on a stable dose of voglibose.

4. SUBJECT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures

2. Male or female who are ≥20 years of age

3. Women of child-bearing potential who comply with the following:

   - Use an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the study

   - Have a negative urine pregnancy test at Visit 1

4. Diagnosed with type 2 diabetes

5. Already on voglibose treatment with a steady dosage for at least 8 weeks (one change in voglibose dose to 0.2 mg tid by 4 weeks before is allowable)

6. Fasting C-peptide > 1.0 ng/mL (0.33 nmol/L)

7. FPG ≤180 mg/dL

8. HbA1c ≤8.5%

4.2 Exclusion criteria

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

Endocrine and metabolic disorders

1. Diagnosis of Type 1 diabetes mellitus, known diagnosis of MODY or secondary diabetes mellitus

2. History of diabetic ketoacidosis

3. Symptoms of poorly controlled diabetes including, but not limited to, marked polyuria, polydipsia, and/or greater than 10% weight loss during the 3 months prior to enrolment

4. History of bariatric surgery (ie, any surgery to treat obesity; for example, gastric banding or procedures that involve bypassing or transposing sections of the small intestine). History of liposuction is allowed.

5. Diabetes insipidus

6. Thyroid-stimulating hormone (TSH) values outside normal range

Kidney disorders

7. Calculated Creatinine Clearance <50 mL/min (calculated by Cockroft-Gault formula)

8. Urine albumin: creatinine ratio (UACR) >1800 mg/g (>203.4 mg/mmol)

9. History of unstable or rapidly progressing kidney disease

10. Known condition of familial renal glucosuria

Hepatic disorders

11. Severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >3X upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >3X ULN

12. Total bilirubin >2.0 mg/dL (>34.2 μmol/L)

13. Positive serologic evidence of current infectious liver disease including Hepatitis B viral antibody IgM, Hepatitis B surface antigen and Hepatitis C virus antibody

14. History of drug-induced liver enzyme elevations

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

Cardiovascular disorders

16. Congestive heart failure defined as New York Heart Association (NYHA) class III and IV, unstable or acute congestive heart failure. Note: eligible patients with congestive heart failure should have careful monitoring of their volume status throughout the study.

17. Significant cardiovascular history within the past 6 months prior to the screening visit, defined as: myocardial infarction, unstable angina pectoris, transient ischemic attack, unstable or previously undiagnosed arrhythmia, cardiac surgery or revascularization (coronary angioplasty or bypass grafts), or cerebrovascular accident. In addition, patients who have unstable cardiovascular disease at enrolment in the judgment of the investigator are excluded from the study.

18. Systolic BP ≥170 mmHg and/or diastolic BP ≥100 mmHg as an average value

Hematologic/oncologic disorders/conditions

19. Haemoglobin ≤10 g/dL (≤100 g/L) for men; haemoglobin ≤9.0 g/dL (≤90 g/L) for women

20. History of chronic haemolytic anaemia or haemoglobinopathies (for example, sickle cell anaemia, thalassemia, sideroblastic anaemia)

21. Donation or transfusion of blood, plasma, or platelets within the past 3 months prior to Visit 1

22. History of malignancy within the last 5 years, excluding successful treatment of basal or squamous cell skin carcinoma

Infectious disease/immunologic disorders

23. Known immunocompromised status, including patients who have undergone organ transplantation

Musculoskeletal disorders

24. Creatine Kinase (CK) >3X ULN

25. History of drug-induced myopathy or drug-induced CK elevation

Reproductive status

26. Pregnant or breastfeeding patients

Prohibited medications

27. Treatment combination for diabetes within 12 weeks of Visit 1, except the minimum approved doses of one antidiabetes drug with voglibose

28. Use of insulin within 24 weeks of Visit 1 (with the exception of one temporary period of daily insulin injections no later than 2 weeks prior to the study)

29. Treatment with glucocorticoids equivalent to oral prednisolone ≥10 mg betametasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day within 30 days prior to Visit 1; topical or inhaled corticosteroids are allowed

30. Use of concomitant medication after Visit 1, except voglibose, antihypertensives (other than diuretics and those which may affect the pharmacokinetics of dapagliflozin), statins, warfarin-type anticoagulants and low dose aspirin

Other

31. Any clinically significant abnormality identified on physical examination, ECG or laboratory tests, which in the judgement of the investigator would compromise the patient's safety or successful participation in the clinical study

32. Patients who, in the judgement of the investigator, may be at risk for dehydration

33. Acute or chronic metabolic acidosis

34. History of alcohol abuse or illegal drug use within the past 12 months

35. Involvement in the planning and conduct of the study (applies to both AstraZeneca and Bristol-Myers Squibb staff or staff at the study centre)

36. Previous enrolment or randomisation to treatment in the present study

37. Previous participation in a clinical study with dapagliflozin in which the patient received at least one dose of study medication.

38. Participation in another clinical study during the last 1 month

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Patients will be required to:

1. Abstain from food from 22:00 and from beverages (except water) from 24:00 the night before each visit. Water will not be allowed for 2 hours before each administration of dapagliflozin.

2. Abstain from tobacco/nicotine use from 12 hours prior to each visit and from alcohol intake 24 hours prior to each visit.

3. Abstain from donating blood during the study and for 3 months after the last study day.

5.2 Subject enrolment and randomisation

The Principal Investigator 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#'.

3. Determine subject eligibility. See Sections 4.1 and 4.2

4. Assign eligible subject the unique subject number

If a subject withdraws from participation in the study, then his/her enrolment code/the unique subject number cannot be reused.

5.3 Procedures for handling subjects incorrectly enrolled

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

Where subjects that do not meet the selection criteria are incorrectly started in error or on treatment, or where subjects 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 subject 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 subject 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 product(s)

Dapagliflozin(BMS-512148) are packed into HDPE bottle and supplied by AstraZeneca. For details of the identity of the investigational product see below.

Investigational product	Dosage form and strength	Manufacturer
BMS-512148	Contain 10 mg for dapagliflozin and green, plain diamond shaped and film coated tablet	Bristol-Myers Squibb Company

5.5.2 Doses and treatment regimens

Dapagliflozin 10mg tablet will be administered orally, as a single dose in the morning during fasting conditions. See section 3.1 for further information.

5.5.3 Additional study drug

Not applicable

5.5.4 Labelling

Each packaging and bottle of investigational product will have a label indicating “For clinical study use”.

Details of labelling and packaging of the study drug will be described in a separate document, ‘Procedure of storage conditions for investigational product’.

5.5.5 Storage

All investigational drugs should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified in the document 'Procedure of storage conditions for investigational product'

5.6 Concomitant and post-study treatment(s)

No concomitant medication or therapy will be allowed except for antihypertensives (other than diuretics and those which may affect the pharmacokinetics of dapagliflozin), statins, warfarin-type anticoagulants and low dose aspirin (≤100 mg). If these allowed medications are used they must be administered on a fixed daily dose throughout the study period.

During the wash-out period, concomitant drugs (except antidiabetic agents and glucocorticoids) can be used if medically needed, under the condition that Visit 5 (2nd dapagliflozin administration) will be conducted ≥7 days after the last dose of the concomitant drugs.

During the PK sampling periods (Visits 2 to 4 and Visits 5 to 7), a change of concomitant medications (change of the dose and addition of a new drug) is not be allowed basically, but if it is acutely necessary, the investigators should consult with AstraZeneca.

Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

5.7 Treatment compliance

The administration of all medication (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

5.7.1 Accountability

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

5.8 Discontinuation of investigational product

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

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment

- Adverse Event
- Severe non-compliance to study protocol

Unlike other studies in the development program of dapagliflozin, specific criteria are not predefined since there are only two single dosing in this study.

5.8.1 Procedures for discontinuation of a subject from investigational product

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The Principal Investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4) and study drug should be returned by the subject.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects 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 6.4.3 and 6.4.4) and study drug should be returned by the subject.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the electronic Case Report Form (eCRF Instructions).

The eCRF Instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. Site personnel will enter the data in the eCRFs. The data will then be Source Data Verified, reviewed/ queried and updated as needed. The principal investigator will then sign the eCRF electronically.

When all data have been declared clean and signed by the investigator, the data will be frozen and then locked to prevent further editing. A copy of the eCRF will be archived at the study site when the study has been locked.

6.2 Data collection and enrolment

The following study measurements will be obtained. The timing of these measurements is detailed in the study plan (Table 1). The following 'priority order' will be in effect when more than one assessment is required at a particular time point:

- ECG
- Pulse rate/BP
- Blood samples (PK, safety laboratory measurement)

6.2.1 Medical examination and demographic measurements

Enrolment medical examination and demographic measurements

Each patient will undergo an enrolment medical examination (Visit 1) 7 (±3) days prior to Visit 2. Data to be collected are as follows:

- Recording of demographic data - date of birth, sex, race
- Diabetes History
- Medical/Surgical history, past and current
- Concomitant medication
- A blood sample for standard clinical chemistry and haematology assessments and spot urine sample for urinalysis
- A resting blood pressure and pulse rate measurement
- Urine pregnancy test (only for pre-menopausal women of child-bearing potential). In the event of suspected pregnancy during the study, the test should be repeated.
- Weight (to be recorded in kilograms to one decimal place)

Data listed above are to be recorded at Visit 1. Patients will also be given diet and life-style advice at Visit 1.

Measurements at Visit 2

The following measurements will be performed and recorded only at Visit 2.

- Height (to be recorded in centimetres)

6.2.2 Follow-up procedures

A similar post-study medical examination (excluding the demographic data, height and medical, diabetes and surgical history) will be done at the last visit (Visit 7/follow-up).

6.3 Efficacy – Not applicable

6.4 Safety

It is of the utmost importance that all staffs involved in the study are familiar with the content of this section. The investigator is responsible for ensuring this.

6.4.1 Definition of adverse events

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

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

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

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, 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 (including hospitalisation for tests related to adverse events), except hospitalisation that has been planned before enrolment
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject 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 reporting purposes, all cases of cancer and overdose must be reported immediately using the SAE module of eCRF.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of adverse events

Time period for collection of adverse events

All events will be collected from sampling period 1(Visit2) to the follow-up study (Visit 7). SAE will be collected from the signing of informed consent to follow-up period(Visit 7).

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- the date 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)
- outcome
- treatment required

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE

Maximum intensity will be graded according to the following definitions:

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

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

Causality collection

The Investigator will assess causal relationship between 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?”

Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.

For SAEs causal relationship will also be assessed for other medication. 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 patient or reported in response to the open question from the study personnel: “Have you had any health problems since the previous visit?” 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

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they are clinically significant, fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product, or require the patient to receive specific corrective therapy. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. 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.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AE(s).

Wherever possible the reporting investigator is to use the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

Follow-up of unresolved adverse events

Any AEs that are unresolved at the end of the study or at discontinuation are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.4.4 Reporting of serious adverse events

Investigators and other centre personnel must inform appropriate AstraZeneca representatives via the web based data capture (WBDC) system of any SAE which occurs in the course of the study within one calendar day (i.e., immediately but no later than the end of the next business day) of when he or she becomes aware of it. Follow-up information on SAEs must also be reported by the Investigator(s) within the same time frame.

The AstraZeneca representative will work with the Investigator to compile all the necessary information and ensure that Bristol-Myers Squibb receives a report by day one for all fatal and life threatening SAEs and by day three for all other SAEs. All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s).

If the system is unavailable, the Investigator should contact the AstraZeneca representative immediately recognising that the same reporting time frames still apply. The Investigator is responsible for completing the eCRF as soon as the system becomes available again. The AstraZeneca representative will forward all information relevant to the SAE to Bristol-Myers Squibb Pharmacovigilance via email.

AstraZeneca will provide the information on the serious adverse drug reactions collected domestically and abroad regarding the investigational product to the Head of the study site, Investigators and the regulatory agency as per local requirements. The Head of the study site must submit a written report to the IRB providing the information reported by AstraZeneca.

6.4.5 Laboratory safety assessment

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

The following laboratory variables will be measured:

Clinical chemistry (serum)	**Clinical chemistry (plasma)**
Aspartate Aminotransferase (AST, SGOT)	FPG
Alanine Aminotransferase (ALT, SGPT)	HbAlc
Alkaline Phosphatase (AP)	
Creatine Kinase (CK)	**Haematology**
Total Bilirubin (TB)	Haemoglobin
Blood Urea Nitrogen (BUN)	Haematocrit
Electrolytes:	Red blood cell count
- Sodium	White blood cell count and differential
- Bicarbonate	Platelet count
- Potassium	
- Chloride	**Urinalysis (dipstick)**
- Calcium	Glucose
- Magnesium	Blood [b]
- Phosphorus	Protein
Total protein	Pregnancy test [c]
Albumin	
Uric acid	**Spot Urine Collection**
Serum Creatinine (SCr)	Creatinine
Calculated creatinine clearance (Cockroft-Gault formula) [a]	Albumin
FSH	
TSH	
Hepatitis Screen Panel[d]	

a Creatinine clearance will be calculated by the method of Cockcroft and Gault
b Microscopy wil be performed if dipstick positive for blood.
c Urine HCG pregnancy test for woman of child-bearing potential (HCG minimum sensitivity of 25 IU/L) (dipstick analyzed at the study centre).
d Includes Hepatitis B viral antibody IgM, Hepatitis B surface antigen and Hepatitis C virus antibody.

For blood volume see Section 7.1

6.4.6 Physical examination

A physical examination includes the following: cardiovascular, lungs, abdomen, and extremities; and any organ systems pertinent to the subject's signs, symptoms or adverse events.

Baseline data for physical examination is collected at Visit 2, and new findings at the following physical examinations are recorded as change from baseline.

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

A 12-lead ECG must be performed at Visit 2 (Day 0) and Visit 7.

A 12-lead ECG will be taken after the subject has been lying down resting. The ECG will be evaluated by the investigator and entered as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal" the investigator should document the specific abnormality.

6.4.8 Vital signs

Sitting Blood Pressure (BP) and heart rate

One heart rate measurement will be taken after the patient has been sitting and resting for at least 5 minutes and before blood samples are taken. The heart rate measurement will be followed by 3 blood pressure measurements, using a standardized cuff adapted to the size of the patient's arm. All 3 readings have to be recorded. For analysis the average of the 3 blood pressure readings will be used. blood pressure readings will be taken with the patients comfortably in a seated position with the arms raised to the level of the heart and in a supported position. All readings should be recorded as accurately as possible and the same blood pressure machine should be used for all assessments for a given patient.

6.4.9 Body weight and height

- The subject's weight will be recorded in kilograms (kg), to one decimal place. Measurement of weight should be performed with the subject dressed in indoor clothing, shoes removed, and bladder empty. Subjects should be weighed on the same scale at all visits.

- The subject's height will be recorded in centimetres. Measurement of height should be performed with the subject's shoes removed. The subject's knees should be straightened, head held erect, and eyes forward.

6.5 Patient reported outcomes (PRO) – Not applicable

6.6 Pharmacokinetics

6.6.1 Collection of samples

Blood samples (3 mL) for determination of dapagliflozin in plasma will be taken at the times presented in the study plan (Table 1).

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

For blood volume see Section 7.1.

6.6.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by AtlanBio Route de Saint-André des EauxZ.I de BraisB.P 4030944605 SAINT-NAZAIRE Cedex FRANCE *on* behalf AstraZeneca, using HPLC-MS method after solid phase extraction. The lower limit of quantification LLOQ of dapagliflozin in plasma is 1.0 ng/mL.

6.7 Pharmacodynamics – Not applicable

6.8 Pharmacogenetics – Not applicable

6.9 Health economics – Not applicable

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The samples will be processed by a central laboratory vender SRL Medisearch Inc.. Central laboratories will supply materials for blood sampling for the laboratory assessments and provide sample transportation.

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

Table 2 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	7.0	7	49
	Haematology	2.0	7	14
	FPG	2.0	7	14
	HbA1c	2.0	7	14
	Hepatitis Screen Panel	10	1	10
Pharmacokinetic		3.0	30	90
Total				191

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses.

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 subject 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 at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

If a subject 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.

A subject who withdraws their consent is withdrawn from further study participation as collection of the biological samples is an integral part of the study.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, 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 subject 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 ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications.

8.2 Subject data protection

The Master Informed Consent Form will explain that: Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. ·Subject data will be maintained confidentially in accordance with national data legislation. For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority or an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history. ·All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code).

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 subjects. The Head of the study site will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The head of the study site must submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca before enrolment of any subject should into the study.

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

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

The protocol should be re-approved by the IRB annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, to be approved by the national regulatory authority or a notification to the national regulatory authority is to be 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 SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

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

If any new information on the study medication becomes available which may influence the decision of the subject to continue the study, the investigator(s) should inform the subject of such information immediately, record this in a written form, and confirm with the subject if he or she wishes to continue the participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they should revise it immediately (Refer to Section 8.5). The investigator(s) should explain the updated Informed Consent Form to the subjects even if the subjects have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

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 it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

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 International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first subject 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 subjects 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 subject 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 the WBDC system(s) 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 subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

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 data are any data generated as a result of the subject's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records.

Original data recorded on the CRFs and regarded as source data are as follows.

- Reason for therapy or medication
- Any Comments on CRF

- Evaluation for inclusion/exclusion criteria on CRIT
- Adverse Event (Yes/No, Maximum intensity, Serious, Treatment required, Outcome, Causality)
- Description of AE on Serious Adverse Event form
- Main reason for premature discontinuation

9.3.2 Direct access to source data in Japan

The Head of the institution and the Principal Investigator/sub-investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the CRFs against source data before collecting the CRFs to ensure accuracy and completeness of documentation, and assure that the Principal Investigator/sub-investigator has submitted the CRFs to AstraZeneca. If the investigator wishes to amend the collected CRFs, the monitor will ensure that the Principal Investigator/sub-investigator has documented the amendment in writing (signed and dated) and provided this to AstraZeneca.

9.4 Study agreements

The Principal Investigator at each/the centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

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

9.4.1 Archiving of study documents

(i) **Study files.** AstraZeneca will provide the Principal Investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca) should be retained in this file by the Principal Investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca's auditor, regulatory authorities, or IRB.

(ii) **Period of record retention**. The study site (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (eg, source document such as medical records, contract, signed consent form). Essential documents should be

retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca. However this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca. AstraZeneca should notify the head of the study site in writing when the study related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

9.4.2 Deviation from the clinical study protocol in Japan

Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the patients or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical trial (e.g. changes to the organisation/structure of the sponsor, the name/department name of the medical institution, the address or phone number of the medical institution or the sponsor, the job title of the investigator, and monitors). In such case, the principal investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca and the head of the study site and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca should be obtained via the head of the study site.

The investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the patients or for other medically compelling reason, the investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

9.5 Study timetable and end of study

The end of the study is defined as ‘the last visit of the last subject undergoing the study’.

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

Planned duration of the study:

Study period: January 2010 – April 2010

Registration period: January 2010 – April 2010

Discontinuation or suspension of the whole study programme

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator, the head of the institution, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

The Principal Investigator/sub-investigator will immediately notify the decision to the subjects, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

Completion of the study

Upon terminating the study, the Principal Investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the institution's rules. The head of the study site, who is informed of the termination by the investigator, will provide a written notification of the results to the IRB and AstraZeneca.

10. DATA MANAGEMENT BY ASTRAZENECA DATA MANAGEMENT CENTRE

Data management will be performed by AstraZeneca Data Management Centre staff.

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the Bristol-Myers Squibb Drug Dictionary. All coding will be performed by the Medical Coding Team at Bristol-Myers Squibb.

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

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

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

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

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable).

Data Management will ensure that the data collection tool will be tested / validated as needed. External data reconciliation will be done with the clinical database as applicable.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s) – Not applicable

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and 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/vital signs/ECG data will be performed for identification of OAEs.

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

11.3 Calculation or derivation of patient reported outcome variables – Not applicable

11.4 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic (PK) analyses will be performed at AstraZeneca R&D. The actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined:

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve from zero to infinity (AUC), area under the plasma concentration-time curve from zero to last measurable point (AUC_{0-t}), oral plasma clearance (CL/F).

11.5 Calculation or derivation of pharmacodynamic variable(s) – Not applicable

11.6 Calculation or derivation of pharmacogenetic variables – Not applicable

11.7 Calculation or derivation of health economic variables – Not applicable

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

The classification of subjects into analysis sets will be made prior to the clean file meeting.

12.1.1 PK analysis set

All subjects who received at least one dose of investigational product and whose PK data are available without the protocol violations or deviations relating to inclusion/exclusion criteria, PK sampling and concomitant medications will be included in the PK analysis set.

12.1.2 Safety analysis set

All subjects who received at least one dose of investigational product will be included in the safety population.

12.2 Methods of statistical analyses

The statistical analyses will be performed by Statistics & Programming department, AstraZeneca K.K., Japan.

The coefficient of variation (CV) will be calculated as $100 \times \sqrt{\exp(s^2) - 1}$, where s is the standard deviation of the data on a log scale.

12.2.1 Demographic data

Age, sex, weight, height and BMI will be summarised using appropriate descriptive statistics.

12.2.2 Plasma concentration data

All plasma concentration of dapagliflozin will be listed by subject and summarised by dosing condition (with voglibose or without voglibose).

The plasma concentration of dapagliflozin at each time point will be summarised using the following descriptive statistics.

- Number of subjects

- Number of observations above LOQ
- Geometric mean
- CV
- Arithmetic mean
- SD
- Minimum
- Median
- Maximum

When calculating descriptive statistics, the plasma concentrations of dapagliflozin below LOQ will be substituted by LOQ/2.

The plots of individual and geometric mean plasma concentration of dapaglifolozin over time for each dosing condition will be made.

12.2.3 PK parameter

All PK parameter will be listed by subject and summarised by the dosing condition.

All PK parameters, except for t_{max}, will be summarised using the following descriptive statistics.

- Number of subjects
- Geometric mean
- CV
- Arithmetic mean
- SD
- Minimum
- Median
- Maximum

For t_{max}, the following descriptive statistics will be presented.

- Number of subjects

- Minimum
- Median
- Maximum

The comparison between dosing condition for each PK parameters will be made based on complete case analysis. The pharmacokinetic variables AUC and C_{max} will be log-transformed before analysis. To assess the effect of voglibose on the AUC and C_{max} of dapagliflozin, they will be analysed using a mixed effect ANOVA model including the dosing condition (with voglibose or without voglibose) as fixed effect and patient as a random effect. Estimates and confidence intervals of the difference between the dosing conditions will first be constructed in the log scale. Then the estimates and confidence intervals of ratio of geometric means between the dosing conditions in the original scale will be obtained by taking anti-logarithms. The estimates and 2-sided 90% confidence intervals of the ratio of geometric means will be presented for:

- AUC (with voglibose) /AUC (without voglibose)
- C_{max} (with voglibose) / C_{max} (without voglibose)

It will be concluded that there is no pharmacokinetic drug-drug interaction if the confidence interval falls within 0.8 – 1.25 for AUC and C_{max} of dapagliflozin. No adjustment for the multiplicity will be made.

The comparison between the dosing conditions for other PK parameters will be made in descriptive manner.

12.2.4 Safety data

All safety data will be listed for each individual patients and summarised across all patients by dosing conditions. The comparison between the dosing conditions for safety data will be made in descriptive manner.

All AEs during each PK sampling period and wash-out period will be listed and summarised by the System Organ Class and Preferred Terms assigned to the events using the Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Furthermore, listings of serious adverse events and adverse events that led to withdrawal will be made and the number of patients who had any adverse events, serious adverse events, adverse events that led to withdrawal, and adverse events with severe intensity will be summarised. If appropriate, adverse drug reactions will be summarised by the System Organ Class and Preferred Term assigned to the event using the MedDRA.

For the quantitative safety variables, the observed value and the changes from baseline at each time point will be summarised using the following descriptive statistics.

- Number of subjects

- Arithmetic mean
- SD
- Minimum
- Median
- Maximum

For all quantitative safety variables, the baseline will be the pre-dose value at Visit 2.

The number of patients in each category of qualitative safety variables at each time point will be summarised.

Laboratories values outside the reference range will be listed.

12.3 Determination of sample size

Based on Studies MB102005 and MB102026, within subject standard deviation of log(AUC) and log(C_{max}) is expected to be at most 0.095 and 0.2024, respectively. With 20 patients, the 2-sided 90% confidence intervals for ratios AUC (with voglibose) /AUC (no voglibose) and C_{max} (with voglibose) / C_{max} (no voglibose) will fall within 0.8 - 1.25 with power over 99% and 90%, respectively, if voglibose has no true effect on AUC and C_{max} of dapagliflozin. Two (10%) additional subjects are included to account for possible dropouts.

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

12.4 Data monitoring committee variables – Not applicable

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency the investigator may contact the Monitors or the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician/other physician at the AstraZeneca Research and development.

Name	Role in the study	Address & telephone number

13.2 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of dapagliflozin that is considered both excessive and medically important. Once an investigator decides that a particular occurrences is an overdose, it must be reported using the SAE module of eCRF (see Section 6.4.4).

13.3 Pregnancy

All outcomes of pregnancy must be reported to AstraZeneca.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product must be discontinued immediately.

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

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives **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 subject must also be discontinued from the study.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to Bristol-Myers Squibb Pharmacovigilance within 3 days, see Section 6.4.4.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

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Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

An Open-label, Multi-centre, Drug-drug Interaction Study to assess the effect of Voglibose (0.2 mg tid) on the Pharmacokinetics, Safety and Tolerability of single oral administration of dapagliflozin (10 mg) in Japanese Patients with Type 2 Diabetes

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)

An Open-label, Multi-centre, Drug-drug Interaction Study to assess the effect of Voglibose (0.2 mg tid) on the Pharmacokinetics, Safety and Tolerability of single oral administration of dapagliflozin (10 mg) in Japanese Patients with Type 2 Diabetes

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ASTRAZENECA SIGNATURE(S)

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An Open-label, Multi-centre, Drug-drug Interaction Study to assess the effect of Voglibose (0.2 mg tid) on the Pharmacokinetics, Safety and Tolerability of single oral administration of dapagliflozin (10 mg) in Japanese Patients with Type 2 Diabetes

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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.

AstraZeneca Research and Development site representative

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 havingg 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.

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.

Appendix D
Instruction For Sampling, Handling and Shipment of Pharmacokinetic Samples

1. TYPES OF SAMPLE

In this study, blood samples will be collected and transported to the bioanalytical laboratory in France to analyse the concentration of dapagliflozin in plasma.

Any biological samples identified as Infectious Category A materials (see IATA 6.2 Regulations Guidance in Appendix C) are not allowed to be shipped (see Section 7.3 in the study protocol).

2. SAMPLING AND HANDLING

2.1 Sample Device

Disposable needles and disposable tubes shall be used. Needles and catheters will be prepared at each study centre, and sampling tubes will be prepared by AstraZeneca K.K.

2.2 Blood Sampling

Blood samples (3 mL per sample) will be collected by direct venipuncture or through an indwelling catheter into a properly labelled 3.0 mL tube (Vacutainer plastic tubes for 3 mL BD (Becton Dickinson, Ref.no. 367859)) with K2EDTA as the anticoagulant. If a catheter is used for blood collection, then approximately 1 mL of blood should be withdrawn initially and discarded. Immediately after collection, each blood sample will be gently inverted 8-10 times for complete mixing with the anticoagulant. Within 60 minutes, each blood sample will be centrifuged at room temperature for 15 minutes at approximately 1000 x g to separate plasma. The separated plasma will be transferred to an appropriately labelled transfer 4 mL polypropylene tube (SImport Plastics, Cryovial™ ,Ref.no. T310-4A or NUNC cryovials) within 15 minutes of centrifugation. Samples must be stored immediately at or below -20°C in an upright position.

2.3 Labelling

On each sample tube the label with pre-printed information, including the sample identification, will be attached. The label can only be used for the intended sample and the pre-printed information must not be changed.

3. SHIPMENT

Samples will be packed in the dedicated package supplied by AstraZeneca K.K., and the appropriate requisition forms must be completed by the investigators or delegates.

Samples will be shipped by SRL Medisearch Inc. via its agreed courier to the laboratory. Where possible, the samples would be shipped in batches and would be coordinated to arrive within working hours of the receiving laboratory site.

Details of sample packing, documentation and shipping conditions are specified in the laboratory manual.

3.1 Bioanalytical laboratory

Appendix E
New York Heart Association Functional Class

1. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS

I. Patients without limitation of physical activity. Ordinary activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

II. Patients with slight limitation of physical activity who are comfortable at rest. Ordinary activity results in palpitation, dyspnea, or fatigue.

III. Patients with marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.

IV. Patients with inability to carry on any physical activity without discomfort. Symptoms may be present at rest.

Clinical Study Protocol: Supplement A

Drug Substance	Dapagliflozin
Study Code	D1692C00002
Supplement Edition Number	1
Supplement Date	

Supplement A
Investigators and Study Administrative Structure

STAFF AT STUDY SITE(S)

Centre No.	**Centre address**	**Name** (First name, Last name)	**Qualifications**	**Present position**	**Role in the study**

ASTRAZENECA STUDY PERSONNEL

Address	**Name** (First name, Last name)	**Qualifications**	**Present Position**	**Role in the study**

Address	**Name** (First name, Last name)	**Qualifications**	**Present Position**	**Role in the study**

OTHER PARTICIPANTS

Organisation and address	Role in study