AstraZeneca

Clinical Study Protocol

Drug Substance	Dapagliflozin
Study Code	D1690L00067
Version	3
Date	07 June 2016

Effects of Dapagliflozin Compared with Glimepiride on Body Composition in Patients with Type 2 Diabetes Inadequately Controlled with Metformin

Sponsor:

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VERSION HISTORY

Version 3.0, 07 June 2016
Protocol Synopsis (National Co-ordinating Investigator, NCI): The national co-ordinating investigator was changed and the name, address, e-mail were updated to reflect the new NCI. Protocol Synopsis (No. of study sites and timeline): the number of study sites was increased from 15 to 17, and the estimated date of last subject completed was updated in accordance with the current recruitment status. List of Abbreviations and Definition of Terms: a few abbreviations were added. Section 2.2 (Secondary objectives): A secondary objective was added to evaluation the effect on lean volume of dapagliflozin compared to glimepiride in subjects with type 2 subjects. Accordingly, changes in lean mass from baseline using Dual Energy X-ray Absorptiometry (DXA) scan (baseline, 52 weeks) was added as the outcome measure for the additional objective. Section 3.1 (Inclusion criteria): The HbA1c range for the inclusion in the study was modified to reflect the HbA1c range found in patients with type 2 diabetes and insufficient glycemic control in the real-world clinical setting. Section 3.2 (Exclusion criteria): Patients with any kind of surgery using foreign metallic materials was added as an exclusion criterion to facilitate accurate readings of DXA scan results. Section 3.3 (Subject enrolment and randomization): The word ‘approximately’ was added as it refers to an estimated number of enrolled patients. Section 4 (Study plan and timing of procedures): The word ‘CT’ was added for clarification; and the HbA1C range was modified to reflect the latest change in the inclusion criteria of the study. Section 5.1.1 (Efficacy assessments – DXA): Evaluation of lean mass was added as it was added as a secondary objective. Section 5.1.2 (CT): The number and location of slices required for analysis was changed for improved CT analysis. Section 5.1.5 (Pulse and Blood Pressure): Changes were made to allow the pulse, blood pressure, and blood sample collection to be performed in any order. Section 5.2.3 (Hypoglycemic event): The error in cross-reference was corrected.

Section 6.3.3 (Variable): The error in cross-reference was corrected.

Section 6.9 (Investigational product and other treatments): This section was moved to a separate level-1 heading, Section 7.0 and thereafter.

Section 7.7.1 (Prohibited medication): The error in cross-reference was corrected.

Section 7.5.2 (Analysis of the secondary variable): The analysis method for the additional secondary variable, 'changes in lean mass from baseline using DXA from baseline to 52 weeks,' was added.

Version 2.0, 2nd November 2015

Section (Protocol Synopsis - Timeline): The timeline was modified to reflect more realistic timeline.

Section (Protocol Synopsis – Objectives): 75g-OGTT related endpoint was deleted, and the secondary endpoints in the secondary objective no. 4 was moved to the secondary objective no. 1.

Figure 1. Study Flow-chart: The study flow chart was modified to reflect the changed allowed dose range of Metformin prior to randomization.

Section 3.1 (Inclusion criteria): Metformin dose range to be eligible for participation in the study was modified to reflect the practical dose of Metformin which patients with type 2 diabetes who is controlled inadequately with Metformin monotherapy take in real clinical practice; and specific descriptions to clarify eligibility criteria for Women of Childbearing potential (WOCBP).

Section 3.2 (Exclusion criteria): Breast-feeding patients as an exclusion criterion and statements that unstable body weight will be judged by investigator, and alcohol and drug abuse will be judged by physician, were added; Exclusion criteria were made more specific for clarification.

Table 1. Study Flow-Chart: Visit window for screening visit was changed to 7 days based on routine practice. Urinalysis was added to be performed on every visit. Candidates for pregnancy test was specified. The DPP-4 inhibitor as a rescue medication was specified as sitagliptin.

Section 5.1.2 (CT): The CT imaging method was modified to improve the reproducibility and reliability of CT scan results.

Section 9.2 Subject Data Protection: Detailed description was added for clarification.

Section 9.4 Informed Consent: Detailed description regarding the environment in which the

consent should be obtained was added.

Version 1.0, 31st June 2015
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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PROTOCOL SYNOPSIS

Effects of Dapagliflozin Compared with Glimepiride on Body Composition in Patients with Type 2 Diabetes Inadequately Controlled with Metformin

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Study site(s) and number of subjects planned

No. of total randomized subjects 120
No. of total enrolled subjects approximately 160
No. of study sites 17

Study period		Phase of development
Estimated date of first subject enrolled	4Q 2015	IV
Estimated date of last subject completed	4Q 2017	

Study design

12-months, randomized, open-label, parallel-group, multi-centres phase IV study

Objectives

Primary Objective:	Outcome Measure:
To evaluate the effect of dapagliflozin on body composition in Korean T2DM subjects.	Changes in total body fat mass from baseline using Dual Energy X-ray Absorptiometry (DXA) scan in 52 weeks after the start of the treatment

Secondary Objective:	**Outcome Measure :**
Evaluate the efficacy in improving glycaemic control of dapagliflozin compared to glimepiride in subjects with type 2 diabetes.	The change in HbA1c levels from baseline to 52 weeks (baseline, 12, 24, 36 and 52 weeks)
	The proportion of Subjects achieving a glycemic response, defined as HbA1c <7.0% at Week 52
	The change in FBS levels from baseline to 52 weeks (baseline, 4, 12, 24, 36 and 52 weeks)
Evaluate the effect on body weight of dapagliflozin compared to glimepiride in subjects with type 2 diabetes.	Changes in body weight, waist circumference, BMI from baseline (baseline, 4, 12, 24, 36 and 52 weeks)
Evaluate the effect on blood pressure of dapagliflozin compared to glimepiride in subjects with type 2 diabetes.	Changes in SBP and DBP from baseline (baseline, 4, 12, 24, 36 and 52 weeks)
Evaluate the effect on adipose tissue and lean volume of dapagliflozin compared to glimepiride in subjects with type 2 diabetes.	Changes in abdominal VAT and SAT volume, VAT/SAT ratio using abdominal CT from baseline (baseline, 52 weeks)
	Changes in lean mass from baseline using Dual Energy X-ray Absorptiometry (DXA) scan (baseline, 52 weeks)
Evaluate the effect on insulin resistance of dapagliflozin compared to glimepiride in subjects with type 2 diabetes.	Changes in high-sensitivity CRP (hsCRP) and adiponectin from baseline (baseline, 52 weeks)

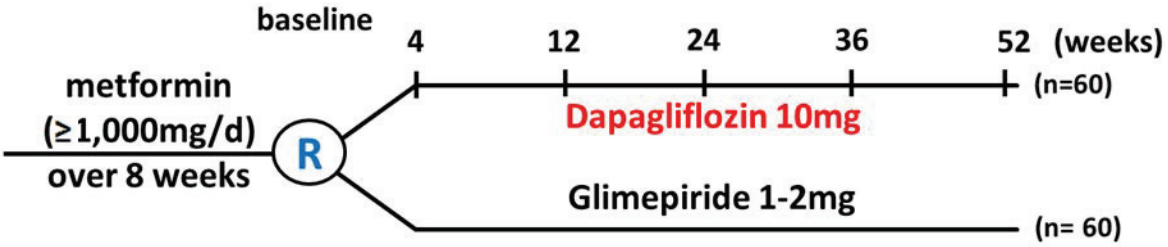
Safety Objective:	**Outcome Measure :**
Evaluate the safety of dapagliflozin and glimepiride	Changes in CBC, electrolytes, lipid, urinalysis from baseline (baseline, 4, 12, 24, 36 and 52 weeks)
	Number, frequency and proportion of Subjects exposed to adverse events
	Number, frequency and proportion of Subjects exposed to hypoglycemic events

Target subject population

The study population of this study consists of patients with type 2 diabetes who are 19 - 75 yrs old male or female with HbA1c ≥7.0 and <10.0% in recent 4 weeks.

Altogether 120 patients in 17 study sites will be randomized to this study.

Duration of treatment



Investigational product, dosage and mode of administration

Investigational Product

Dapagliflozin tablets, 10 mg, administered orally, once daily as add-on to metformin 1000 mg.

Comparator

Glimepiride tablets, 1 mg, administered orally 1 or 2 tablets (1mg or 2mg) as add-on to metformin 1000 mg will be used at a dose of 1 to 2 mg/day with the up-titration. Glimepiride dose can be down-titrated at any time to prevent hypoglycemia.

Statistical methods

The full analysis set will included all randomized subjects who receive at least one dose of study medication during the 52 weeks treatment period who have a non-missing baseline value and at least one post-baseline value for primary efficacy variable. Baseline demographic data will be presented in a descriptive manner. Primary endpoint, change in total body fat mass in each treatment arm, will be analyzed with an analysis of covariance (ANCOVA) model. As for the other endpoints, mixed model repeated measures (MMRM) or ANCOVA will be used for continuous variables or logistic regression for binary variable. If any outcome variables are inappropriately distributed, non-parametric methods will be used accordingly. The statistical significance levels for secondary endpoints will not be adjusted for multiple hypothesis testing and will be interpreted only descriptively.

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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
A1C	Glycated hemoglobin
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
BP	Blood Pressure
CBC	Complete Blood Count
CK	Creatinine Kinase
CPMP	Committee for Proprietary Medicinal Products (EU)
CRF	Case Report Form
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic Acid
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	DTSQ Change Version
DTSQs	DTSQ Status Version
DXA	Dual Energy Xray Absorptiometry
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
FBG	Fasting Blood Glucose
FDA	Food and Drug Administration (US)
FFA	Free Fatty Acid

Abbreviation or special term	Explanation
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDL-C	High-density Lipoprotein Cholesterol
HRT	Hormone replacement Therapy
ICH	International Conference on Harmonisation
IP	Investigational Product
LDL-C	Low-density Lipoprotein Cholesterol
LIMS	Laboratory information management system
LOCF	Last Observation Carried Forward
LSLV	Last Subject Last Visit
N.B.	Nota Bene, mind you
OAD	Oral Antidiabetic Drug
OAE	Other Significant Adverse Event
pCRF	Paper Case Report Form
PGx	Pharmacogenetic research
PI	Principal Investigator
PK	Pharmacokinetics
PPG	Postprandial Plasma Glucose
PPG AUC	Postprandial Glucose Area Under the Curve
PRO	Patient-reported Outcome
SAE	Serious Adverse Event (see definition in Section 6.2).
SDT	Study Delivery Team
SGLT1	Sodium-dependent Glucose Transporter 1
SGLT2	Sodium-dependent Glucose Transporter 2
SU	Sulphonylurea(s)
TG	Triglyceride
TSH	Thyroid-stimulating Hormone
UACR	Urine Albumin:Creatinine Ratio
ULN	Upper Limit of Normal
WBDC	Web Based Data Capture
WOCBP	Women of child bearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Metformin is recommended as a first-line therapy for patients with type 2 diabetes (T2DM). When glycemic control deteriorates, patients with T2DM usually require additional anti-diabetic agents to control glycemia. Sulfonylureas (SUs) such as glimepiride are commonly added to metformin as a second-line treatment in clinical practice when metformin monotherapy cannot adequately control glycemia. However, SUs are frequently associated with unwanted side effects such as weight gain and hypoglycemia.

Therefore, in the present study, we would like to study the effect of dapagliflozin treatment for 52 weeks on body composition in Korean T2DM subjects whose average body mass index (BMI) is around 25 kg/m2. The aim of this study is to compare the influence of dapagliflozin on body composition such as total-body fat mass (FM), abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) volume compared with that of glimepiride. We expect that dapagliflozin treatment will decrease total body weight (TBW), and FM, whereas glimepiride increase them. We speculate in the present study that relative changes in body composition (i.e. fat mass vs. lean mass, VAT vs. SAT) may differ from those of the studies in Caucasians. In accordance with the changes of body composition, we predict that not only insulin resistance but also insulin secretion will improve in the dapagliflozin treatment group.

Until now, there has not been any comparative study about the influences of dapagliflozin vs. glimepiride in this area. Considering SUs are widely used in Asians, especially in Koreans, comparison of dapagliflozin vs. glimepiride on the changes of body composition, and insulin resistance and insulin secretion will give an important clinical implication in the management of diabetes, particularly in non-obese Koreans.

1.2 Rationale for study design, doses and control groups

Parallel group study design was chosen. In order maintain the practicality of the phase IV study, open label design of study drug delivery was chosen. The reading of the DXA scans will be conducted by one expert in blinded manner.

Glimepiride is the most frequently used SUs in Korea and therefore this was chosen as comparator.

Dapagliflozin treatment will be associated with reduction of total body FM, BW, abdominal VAT and SAT volume compared with glimepiride.

1.3 Benefit/risk and ethical assessment

Dapagliflozin, a newly developed sodium-glucose cotransporter 2 (SGLT2) inhibitor, improved glycemic control in patients with T2DM when used as monotherapy or as add-on to metformin [1,2]. SGLT2 inhibitors can reduce hyperglycemia by increasing urinary glucose

excretion [3]. Since the mechanism of SGLT2 inhibitors is independent of insulin action, dapagliflozin treatment is associated with a low risk of hypoglycemia as well as moderate weight loss compared with SUs treatment [4].

Recently, Bolinder et al. [5] have shown that dapagliflozin treatment was associated with reduction in TBW, waist circumference, total-body FM, abdominal VAT and SAT volume in patients with T2DM. In this study of obese Caucasian subjects whose average BMI was 32 kg/m2, the two-thirds of weight loss observed with dapagliflozin treatment was attributable to the reduction in total fat mass as measured by DXA, and moreover, dapagliflozin significantly decreased both abdominal VAT and SAT volumes as measured by magnetic resonance spectroscopy. However, the influence of dapagliflozin on change of body composition has not been studied in Asians, who have lower BMI and relatively higher proportion of visceral fat mass compared to Caucasians. Recent data from the 2011 Korea National Health and Nutrition Examination Survey showed that about half of T2DM subjects in Korea are non-obese, even with obesity defined as a BMI of more than 25 kg/m2 [6]. Moreover, Asians appear to have the high proportion of body fat and prominent abdominal obesity compared to Caucasians with similar BMI values [7,8].

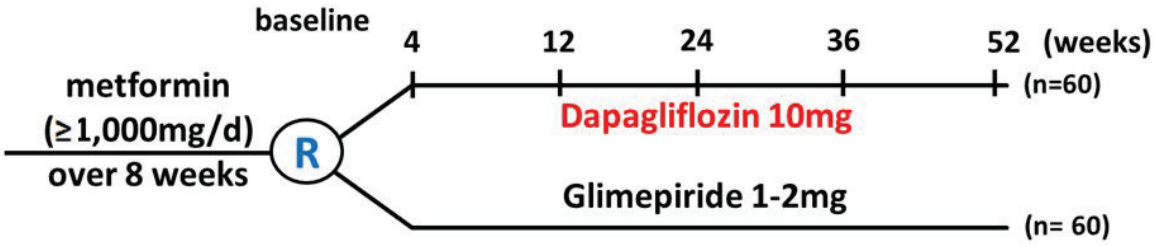
While both insulin resistance and β-cell dysfunction are important components in the pathophysiology of T2DM, the relative contributions of these two factors appear to be variable in different populations [9]. In Asians, the contribution of impaired β-cell function has been suggested to play a more crucial role in the pathogenesis of T2DM compared with Caucasians. In a series of analysis of recent pancreatectomized samples from a Korean university hospital, the pancreatic β-cell mass in T2DM subjects was significantly reduced compared with BMI-matched normal subjects, and β-cell area correlated with some parameters of β-cell function [10,11]. This might be a reasonable explanation for the fact that insulin secretagogues such as SUs are popular anti-hyperglycemic treatments in Asian diabetic patients.

Compared with SUs, we do not know much about the influence of dapagliflozin on insulin secretion in patients with T2DM. A recent study showed that dapagliflozin treatment had a beneficial effect on insulin resistance, but insulin secretion with only borderline significance [12]. In this study, dapagliflozin treatment was associated with improved insulin resistance which was evidenced by the reduction in TBW as well as a significant increase in glucose disappearance rate during hyperinsulinemic euglycemic clamps. The borderline increase in insulin secretion might be secondary to the improvement of insulin resistance. However, it has not been thoroughly studied yet.

1.4 Study Design

This is a 52 weeks, randomized, open-label, parallel-group, multi-centres phase IV study. Participants will be randomized 1:1 to receive dapagliflozin 10 mg qd or glimepiride 1~2 mg qd in an open-label manner for 12 months as add-on to metformin 1000 mg.

Figure 1 Study Flow Chart



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To evaluate the effect of dapagliflozin on body composition in Korean T2DM subjects.	Changes in total body fat mass from baseline using DXA scan in 52 weeks after the start of the treatment

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
To evaluate the efficacy in improving glycaemic control of dapagliflozin compared to glimepiride in subjects with type 2 diabetes.	The change in HbA1c levels from baseline to 52 weeks (baseline, 12, 24, 36 and 52 weeks)
	The proportion of Subjects achieving a glycemic response, defined as HbA1c <7.0% at Week 52
	The change in FBS levels from baseline to 52 weeks 52 weeks (baseline, 4, 12, 24, 36 and 52 weeks)
Evaluate the effect on body weight of dapagliflozin compared to glimepiride in subjects with type 2 diabetes.	Changes in body weight, waist circumference, BMI from baseline 52 weeks (baseline, 4, 12, 24, 36 and 52 weeks)
Evaluate the effect on blood pressure of dapagliflozin compared to glimepiride in subjects with type 2 diabetes.	Changes in SBP and DBP from baseline 52 weeks (baseline, 4, 12, 24, 36 and 52 weeks)
Evaluate the effect on adipose tissue and lean volume of dapagliflozin compared to glimepiride in subjects with type 2	Changes in abdominal VAT and SAT volume, VAT/SAT ratio using abdominal CT from baseline (baseline, 52 weeks)

diabetes.	Changes in lean mass from baseline using Dual Energy X-ray Absorptiometry (DXA) scan (baseline, 52 weeks)
Evaluate the effect on insulin resistance of dapagliflozin compared to glimepiride in subjects with type 2 diabetes.	Changes in hsCRP and adiponectin from baseline (baseline, 52 weeks)

2.3 Safety objectives

Safety Objective:	**Outcome Measure :**
Evaluate the safety of dapagliflozin and glimepiride.	Changes in CBC, electrolytes, lipid, urinalysis from baseline 52 weeks (baseline, 4, 12, 24, 36 and 52 weeks)
	Number, frequency and proportion of Subjects exposed to adverse events
	Number, frequency and proportion of Subjects exposed to hypoglycemic events

2.4 Exploratory objectives

Not applicable

3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

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

3.1 Inclusion criteria

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

1. Adults with T2DM (Male or female, ≥ 19 and ≤ 75 yrs)
2. Patients in insufficient glycemic control (HbA1c ≥ 7.0% and ≤ 10.0% in recent 4 weeks)
3. Patients with an unchanged dose of metformin (≥ 1,000 mg/day) for ≥ 8 weeks prior to randomization
4. Written informed consent

5. WOCBP must take precautions to avoid pregnancy throughout the study and for 4 weeks after intake of the last dose.

   – WOCBP must have a negative urine pregnancy test at screening visit WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal.

   – WOCBP must be willing to use a medically accepted method of contraception that is considered reliable in the judgment of the Investigator.

3.2 Exclusion criteria

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

1. Type 1 diabetes or history of diabetic ketoacidosis

2. Pregnant or breast-feeding patients

3. eGFR < 60 mL/min/1.73 m^2 (MDRD) on visit 1.

4. Indication of active liver disease (AST/ALT/total bilirubin > 3 X upper limits of normal) on visit 1.

5. Acute coronary syndrome, stroke or TIA within 3 months prior to randomization

6. Bariatric surgery within 2 years; treatment of anti-obesity drugs 3 months prior to randomization; any treatment leading to unstable body weight. (Unstable body weight is considered reliable in the judgment of the Investigator.)

7. Any kind of surgery using foreign metallic materials

8. History of bladder cancer or history of radiation therapy to the lower abdomen or pelvis at any time

9. History of any other malignancy within 5 years (with the exception of successfully treated non-melanoma skin cancers)

10. History of alcohol or drug abuse judged by physician within 3 months prior to randomization

11. Concomitant participation in any other clinical study.

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

3.3 Subject enrolment and randomization

120 subjects meeting all inclusion and none of the exclusion criteria will be randomized to the study. Estimated number of enrolled patients is approximately 160.

Subjects will be in open label treatment.

Subjects who discontinue the study will not be replaced.

The E-code is the only subject identification number to be used in CSRs and high level documents.

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

The Investigator(s) 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 code.
3. Determine subject eligibility.
4. Randomize only eligible subjects

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

Randomization will be conducted strictly sequentially as subjects become eligible for randomization.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Biostatistics group in CRO has the responsibility to generate the randomization scheme. The randomization scheme in blocks will be generated by computer software incorporating a random number generator. The randomization scheme can be balanced in blocks across the study.

3.6 Methods for ensuring blinding

Not applicable – This is an open-label study.

3.7 Methods for unblinding

Not applicable – This is an open label study.

3.8 Restrictions

Subjects should be instructed to abstain from all food and recommended not to use tobacco/nicotine products within 12 hours prior to each clinic visit and refrain from alcohol intake 24 hours prior to the visits (drinking water after midnight is allowed). Acceptable concomitant medications can be taken with water only.

Subjects should not take the investigational product and open-label metformin (and rescue medication if applicable) on the morning of the clinic visit.

If a subject comes to a visit without having followed the above instructions, then the subject will be re-scheduled for the entire visit (if possible within allowed time-window).

Subjects who are blood donors should not donate blood from enrolment until 12 weeks following their last dose of randomized treatment.

3.9 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 (including laboratory abnormality or intercurrent illness) which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Major and/or frequent hypoglycaemic events, defined as ≥1 major event or recurring minor events (any recurrent events of hypoglycaemia, as judged by the investigator, not meeting the definition of major hypoglycaemic event)

- Calculated Creatinine-Clearance <60 ml/min or an increase in serum creatinine of ≥0.5 mg/dl above the baseline value confirmed at a repeated measurement within one week.

- Subject will become pregnant

- Use of (need for) any antihyperglycaemic medication other than investigational product and metformin. Insulin use for up to 14 days total during the study and up to 7 continuous days is permitted only in cases where:

  – Subjects are unable to take oral medications (for example during a gastrointestinal illness),

  – There is a documented illness or infection that requires additional therapy for maintaining glycaemic control.

- Severe non-compliance with the study protocol.

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments), without prejudice to further treatment. A subject that decides to discontinue investigational product 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(s). Adverse events will be followed up (See Section 6) and all study drugs should be returned by the subject.

Randomized subjects who discontinue the study prematurely should immediately stop taking investigational product and complete the procedures described for Visit 7 (End of Treatment Visit), as soon as possible but not later than 7 days after discontinuation of investigational product. DXA and CT measurement should be performed as described for Visit 7.

If a subject is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as ‘Incorrect Enrolment’ (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation. Note that the patient may be offered additional tests to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse continuing participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Study is planned to be conducted according to plan described in Table 1.

This study is a 52-week, multi-centres, randomized, parallel-group, open, Phase IV study. All subjects will be enrolled by recruiting centres (centres treating patients with T2DM). Each enrolled subject will be referred to DXA measurement and abdominal CT scan.

The objectives of the study cover measurements at baseline, 4, 12, 24, 36 and 52 weeks. The primary efficacy end-point is to evaluate the effect of dapagliflozin 10 mg daily in

combination with metformin compared to glimepiride in combination with metformin on body composition in Korean T2DM subjects after 52 weeks of oral administration of open-label treatment.

Subjects with T2DM and inadequate glycaemic control (HbA1c ≥7.0% and <10.0%) with stable metformin monotherapy ≥1000 mg/day for at least 8 weeks prior to enrolment will be eligible to enter the study.

The recruiting investigator will be the main point of contact for the subject and also responsible for the documentation of study data within the eCRF. All subjects do DXA measurement and abdominal scan scheduled to coincide with Visit 2 and Visit 7.

Local evaluation of the DXA will be conducted.

Table 1 Study Plan detailing the procedures

	Screening (Baseline)	Randomi-sation	Treatment				End of Therapy	Rescue Visit[2]
Study weeks	***0wk (-7…0 days)***	***0wk***	***4wks (+/- 7 days)***	***12wks (+/- 7 days)***	***24wks(+/- 7 days)***	***36wks(+/- 7 days)***	***52wks(+/- 7 days)***	***Planned if needed***
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	***R***
Informed consent	O							
Demography	O							
Physical Exam[1]	O		O	O	O	O	O	O
Medical/Surgical History	O							
Diabetes History	O							
12 lead ECG	O						O	
Height	O							
Weight	O		O	O	O	O	O	O
BMI calculation	O		O	O	O	O	O	O
Waist circumflex	O		O	O	O	O	O	O
Pulse, blood pressure (SPB/DBP)	O		O	O	O	O	O	O
FBG	O		O	O	O	O	O	O
HbA1C	O			O	O	O	O	O
CBC	O				O		O	O
AST/ALT/total bilirubin	O			O	O		O	O
BUN/creatinine	O			O	O		O	O
Na/K/Cl	O				O		O	O

Cholesterol/TG/HDL	O						O	O
Pregnancy test for all WOCBP	O							
Urinalysis	O		O	O	O	O	O	O
hsCRP, adiponectin	O						O	O
Inclusion/exclusion criteria	O	O						
Randomisation		O						
Provide diet and life-style counselling		O	O	O	O	O	O	O
DXA[3]		O ***0wk (+0…7days)***					O	
CT[4]		O ***0wk (+0…7days)***					O	
Dispense subject's diary		O	O	O	O	O		O
Review subject's diary			O	O	O	O	O	O
Dispense Investigational product		O	O	O	O	O		O
Drug accountability of Investigational product			O	O	O	O	O	
Dispense Metformin		O	O	O	O	O		
Drug accountability of Metformin			O	O	O	O	O	
Check concomitant medication	O		O	O	O	O	O	O
Prescribe rescue medication[5]			O	O	O	O	O	O

Hypoglycaemic events collection			O	O	O	O	O	O
Adverse Events collection		O	O	O	O	O	O	O
Serious Adverse Events collection	O	O	O	O	O	O	O	O

Physical exam[1] : cardiovascular, lungs, abdomen, head, ears, eyes, nose, throat, and extremities
Rescue Visit[2] **:** The rescue visit should take place as soon as possible but not later than 4 weeks after confirmation of repeated FBG and HbA1C. Rescue medication will be dispensed during rescue visit.
DXA[3] : Standardization and level pre-check will be conducted prior to the start of the study. Whole-body DXA machines regardless of any manufacturer can be used in study sites.
Abdominal CT[4] : 1-cut pre-enhanced abdominal CT scan, standardization will be necessary prior to study. Reading of the scans will be conducted centrally.
Prescribe rescue medication[5]: any marketed sitagliptin in the dosage approved in Korea. Rescue medication should only be prescribed if required. See Section 4.5.

4.1 Screening: VISIT 1

Procedures will be performed according to the Study Plan, see Table 1.

Patients will obtain information regarding the study and sign informed consent for the study before any study related procedures are initiated.

Consented patients will be assessed to ensure that they meet eligibility criteria.

Demography, medical/surgical and diabetes history will be checked, 12 lead ECG will be conducted.

Physical exam will be conducted.

Height will be measured in cm (without shoes), weight in kg (light clothes and without shoes) and waist circumference (in cm). BMI calculation will be conducted. Pulse and blood pressure (SBP, DBP) will be measured.

Laboratory baseline test for efficacy and safety parameters will be conducted: FBG, HbA1c, CBC, AST, ALT, total bilirubin, BUN, creatinine, electrolytes, total cholesterol, triglyceride, HDL-cholesterol, urinalysis, hsCRP, adiponectin. All laboratory assessment will be done in central laboratory. Pregnancy test by dipstick should be performed for all WOCBP.

All serious adverse events occurring after signing the informed consent will be reported.

Concomitant diabetes and other medications will be checked.

Eligible patients will receive an enrolment code.

4.2 Randomization: VISIT 2

Eligibility criteria will be checked.

Subjects will be randomized to the treatment arm. Subjects who do not meet these criteria must not be randomized in the study.

DXA and abdominal CT baseline measurement will be conducted.

Diet and life-style counselling will be given to the subject.

Subjects will be given a diary to record hypoglycaemic events (symptoms).

All subjects will be instructed to constantly follow hygiene to avoid urinary tract infections.

Study drug will be dispensed according to randomisation.1mg glimepiride will be dispensed first to the subjects who are allocated to glimepiride group. Metformin will be dispensed.

All serious adverse events will be reported.

Adverse Events will be collected from subject actually taking the IP.

4.3 Treatment Period: VISITS 3, 4, 5, 6

Physical exam contains measurement of weight, waist circumflex, pulse and blood pressure. BMI calculation will be conducted.

Subject diary will be reviewed for hypoglycaemic events. New diary will be dispensed to the subjects.

Subjects will be followed for laboratory assessment of efficacy and safety according to study plan:

- Visit 3: FBG, urinalysis
- Visit 4: FBG, HbA1c, AST, ALT, total bilirubin, BUN, creatinine, urinalysis
- Visit 5: FBG, HbA1c, CBC, AST, ALT, total bilirubin, BUN, creatinine, electrolytes, urinalysis
- Visit 6 : FBG, HbA1c, urinalysis

All laboratory assessment will be done in central laboratory.

Diet and life-style counselling will be given to the subject.

Concomitant medications will be checked.

Drug accountability of investigational product and metformin will be conducted.

Investigational product and metformin will be dispensed.

In case of glimepiride group, glimepiride can be up titrated to 2 mg to maintain glycemic control at the discretion of the investigator after evaluation of glycaemic control in subjects. Glimepiride can be also down titrated to mitigate recurrent hypoglycaemic events at the discretion of the investigator but 0mg is not allowed. If further hypoglycaemic events occur with meeting the discontinuation criteria after taking the 1mg glimepiride, subjects may be discontinued from investigational product.

All serious adverse events will be reported.

Adverse Events will be collected from subject actually taking the IP.

Subjects will discontinue the study if one major hypoglycaemic event or recurring minor hypoglycaemic events (any recurrent events of hypoglycaemia, as judged by the investigator, not meeting the definition of major hypoglycaemic event) occur.

Randomized subjects who discontinue the study prematurely should immediately stop taking investigational product and complete the procedures described for Visit 7.

4.4 End of Treatment: VISIT 7

Physical exam contains measurement of weight, waist circumflex, pulse and blood pressure. BMI calculation will be conducted.

12 lead ECG will be conducted.

Subjects will be followed for laboratory assessment of efficacy and safety according to study plan FBG, HbA1c, CBC, AST, ALT, total bilirubin, BUN, creatinine, electrolytes, total cholesterol, triglyceride, HDL-cholesterol, urinalysis, hsCRP, adiponectin. All laboratory assessment will be done in central laboratory.

Diet and life-style counselling will be given to the subject.

DXA and abdominal CT measurement will be conducted.

Concomitant medications will be checked.

Drug accountability of investigational product and metformin will be conducted.

Subject diary will be reviewed for hypoglycaemic events.

All serious adverse events and adverse events will be reported and followed up

4.5 Lack of Glycaemic Control, Rescue Therapy

The subjects will receive investigational product during the entire randomized study period. All subjects will also continue to be provided with open-label 1000 mg metformin tablets with instructions to continue open-label metformin treatment for the duration of the study.

Randomized subjects with a central laboratory FBG and HbA1c value meeting the criteria for lack of glycaemic control during treatment period may be eligible to receive open-label, prescribed rescue medication which may allow the subject to remain in the trial. In case of subjects who are taking glimepiride, increase of dose to 2mg should be preceded first for glycaemic control. If there is lack of glycaemic control with meeting the rescue criteria though increase of dose to 2mg, rescue medication should be prescribed.

Rescue therapy is open-label, any marketed sitagliptinin the dosage approved in Korea. Rescue medication should only be prescribed by investigator if required. No other rescue therapy is allowed. Treatment should be according local standards of care and approved prescribing guidance. All rescue decisions will be based on central laboratory fasting plasma glucose (FBG) and HbA1C.

Subjects who meet the following rescue criteria will be considered for rescue medication.

- Week 4 – 8 (excluding week 8) FBG >13.2 mmol/L (240 mg/dL)
- Week 8 – 24 (including week 24) FBG >11.1 mmol/L (200 mg/dL)
- Week 24 – Week 52 (including Week 52) HbA1c >8.0%

Randomized subjects who meet the repeated rescue criteria should be scheduled for a rescue visit. The rescue visit should take place as soon as possible but not later than 4 weeks after confirmation of repeated FBG and HbA1C. Rescue medication will be dispensed during rescue visit.

On rescue visit, following procedures will be conducted;

Physical exam contains measurement of weight, waist circumflex, pulse and blood pressure. BMI calculation will be conducted.

Subjects will be followed for laboratory assessment of efficacy and safety according to study plan FBG, HbA1c, CBC, AST, ALT, total bilirubin, BUN, creatinine, electrolytes, total cholesterol, triglyceride, HDL-cholesterol, urinalysis, hsCRP, adiponectin. All laboratory assessment will be done in central laboratory.

Diet and life-style counselling will be given to the subject.

Concomitant medications will be checked.

Subject diary will be reviewed for hypoglycaemic events.

New diary will be dispensed to the subjects.

All serious adverse events and adverse events will be collected.The subjects will continue their study medication (investigational product and open-label metformin) as before and continue the original schedule for the visits during the remainder of the treatment period. Rescued subjects with central laboratory HbA1c values greater than HbA1c values specified per protocol, for 13 weeks despite rescue medication will be discontinued(Discontinuation criteria no. 1) from the study and referred for additional antihyperglycaemic therapy.

5. STUDY ASSESSMENTS

Web Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.
The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

5.1 Efficacy assessments

5.1.1 Dual Energy X-Ray Absorptiometry (DXA)

Whole-body DXA will be used for the estimation of body composition. The relative attenuation of two different x-ray energies by body tissues produces a three-component model comprising total fat mass.

The DXA scans should be performed to evaluate the total body fat and lean mass according to the manufacturer's manual for the DXA equipment, including the instructions for positioning, scan mode and specific information regarding the regions of interest.

Local evaluation will be done and whole-body DXA machines regardless of any manufacturer can be used in study sites. Standardization and level pre-check will be conducted prior to the start of the study.

5.1.2 CT

The CT scan will be performed using standard clinical scanners to evaluate abdominal VAT and SAT volume.

Subcutaneous and visceral fat will be measured using a Multi-detector CT scan. The scans will be done at 100-120 kV, effective mAs. All the patients will be scanned in the craniocaudal or caudocranial direction while they are lying in the supine position with their arms above their head and legs elevated with a cushion. We will acquire five 5-mm thickness slices at the level of the umbilicus with 25mm and 50mm increment and analyzed for a cross-sectional area of adipose tissue, which was expressed in centimeters squared. Areas will be calculated by multiplying the number of pixels of a given tissue type by the pixel number (pixel density). A post processing software (TeraRecon; TeraRecon, Inc., Foster City, CA) will be used for VAT and SAT volume measurement. The CT attenuation of fat will be defined as ranging from -190 to -30 HU. The parameters studied will include visceral fat amount (V) (cm2), subcutaneous fat amount (S) (cm2), V/V+S (%), and belly outer circumference (cm). Visceral fat was distinguished from subcutaneous abdominal fat by tracing along the fascial plane defining the internal abdominal wall. CT scan will not be conducted to the subjects who have contraindications to this procedure.

5.1.3 Height, Weight and Waist Circumference

Height will be measured without shoes (in cm), weight will be measured with light clothes and without shoes (in kg). All readings should be recorded as accurately as possible and the same scale should be used for all assessments for a given subject.

The waist circumference (in cm) will be measured in the morning before breakfast. The waist circumference is measured midway between the lowest rib and the iliac crest. (WHO Report 1987). Measurement should be made at the end of a normal expiration in a standing position and with measuring tape used in the study site.

5.1.4 BMI

BMI will be computed by AstraZeneca.

BMI = weight/height2 (where weight is measured in kg, and height in metres).

BMI will be calculated using the height measured at enrolment.

5.1.5 Pulse and Blood Pressure

One pulse measurement will be taken after the subject has been sitting and resting for at least 5 minutes. Blood pressure will be measured using a standardized cuff adapted to the size of the subject's arm while the subjects remain comfortably in a seated position with the arms raised to the level of the heart and in a supported position.

5.1.6 Physical Examination

A physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, head and neck including head, ears, eyes, nose and throat). The examination at Visit 1 is regarded as baseline data and new findings at the following physical examinations are recorded as change from baseline. Physical examination will also be performed in case of discontinuation of IP.

5.1.7 Laboratory Efficacy Assessments

5.1.7.1 HbA1C

Blood sample for laboratory measurement of HbA1c will be performed at Visit 1, 4, 5, 6, 7 and rescue visit. Laboratory assessments will be done at central laboratory.

5.1.7.2 Fasting Blood Glucose (FBG)

Blood sample for laboratory measurement of the concentration of glucose in the plasma after the patient has not eaten for 12 hours will be performed at Visit 1, 3, 4, 5, 6, 7 and rescue visit. Laboratory assessments will be done at central laboratory.

5.1.7.3 hsCRP and Adiponectin

Blood sample for laboratory measurement of hsCRP and adiponectin in the plasma after the patient has not eaten for 12 hours will be performed at Visit 1, 7 and rescue visit. Assessment will be done in central lab.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood sample for laboratory measurement will be performed at central laboratory.

Table 2 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Creatine kinase (CK)

5.2.2 12-Lead ECG

A 12-lead ECG will be taken (supine position, standard ECG with a recommended paper speed of 50 mm/second covering at least 6 sequential beats) after the subject has been lying down resting for at least 5 minutes. 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 abnormality should be further specified.

5.2.3 Hypoglycemic Event

The subject will be asked to always self-monitor symptoms suggestive of hypoglycaemia and to register any signs of hypoglycaemia in the supplied diary.

A hypoglycaemic event can be either

- An episode with symptoms and confirmed low glucose.
- An episode with low glucose.
- An episode with symptoms when glucose was not measured.

For the evaluation of hypoglycaemic events special attention will be given to hypoglycaemia as defined in accordance with CPMP guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus, as described below.

- Major hypoglycaemic events, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose value <3.0 mmol/L (<54 mg/dL), and prompt recovery after glucose or glucagons administration.

- Minor hypoglycaemic event, defined as either a symptomatic event with a capillary or plasma glucose value <3.5 mmol/L (<63 mg/dL), and no need for external assistance, or an asymptomatic blood glucose measurement <3.5 mmol/L (<63 mg/dL).

- Events suggestive for hypoglycaemia, with symptoms that the subject experiences as hypoglycaemia and no confirmative measurement.

Data to be collected for each hypoglycaemic event:

- Date of start and stop and time of the day for start

- If symptoms are present or not and which symptoms

- If finger stick value obtained and the plasma glucose value

- Intervention needed for recovery, max intensity, action taken, causality and possible contributing factors

- Time of last drug administration

- Time of last meal

The subject's diary will be reviewed and data regarding hypoglycaemic events transcribed into the eCRFs at each clinical visit. A new diary for the next period will be handed over to the subject. If a major hypoglycaemic event occurs, or more than one minor event since last visit, the subject should contact the investigator. For recording of hypoglycaemic events/symptoms suggestive of hypoglycaemic events as AEs, see Section 6.3.

5.3 Pharmacokinetics

Not applicable.

5.4 Pharmacodynamics

Not applicable.

5.5 Pharmacogenetics

Not applicable.

5.6 Biomarker analysis

Not applicable.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., 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.

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

6.2 Definitions of serious adverse event

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

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

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from subject actually taking the IP throughout the entire treatment period and during the follow-up period until the end of the study. SAEs will be collected from the time at which informed consent is obtained until the end of the study.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study 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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 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 IP (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

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.

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 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

Maximum intensity refers to the complete course of the AE. The patient (parents/legal guardians) will be asked to assess the maximum intensity of the reported AEs according to the following scale:

- 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).

6.3.4 Causality collection

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

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

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: *‘Have you had any health problems since the previous visit/you were last asked?’*, or revealed by observation will be collected and recorded in the eCRF. The question will be put to each patient (or parent/legal guardian) in local language from Visit 2 to the last follow-up telephone contact. 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.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs and other safety assessments will be summarized in the CSR. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value, vital sign or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day ie immediately but no later than 24 hours of when he or she becomes aware of it. The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site within 1 calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie immediately but no later than 24 hours of when he or she becomes aware of it.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the Product Information for the Dapagliflozin Overdose.

6.5 Overdose

The risks associated with over dosage of Dapagliflozin are considered to be small.

In previously conducted clinical studies effects of overdose with dapagliflozin included severe nausea, severe vomiting and rapidly declining blood glucose concentrations. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product should 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 should 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 the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study.

6.7 Management of IP related toxicities

Treatment related toxicity is not expected from dapagliflozin, when used as directed. For overdose, see Section 6.5.

6.8 Study governance and oversight

This section is not applicable.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational Product

Dapagliflozin tablets, 10 mg, administered orally, once daily as add-on to metformin 1000 mg.

Comparator

Glimepiride tablets, 1 mg, administered orally 1 or 2 tablets (1mg or 2mg) as add-on to metformin 1000mg will be used at a dose of 1 to 2 mg/day with the up-titration. Glimepiride dose can be down-titrated at any time to prevent hypoglycemia.

Table 3 Investigational Products

Treatment	Dosage form and strength	Manufacturer
Dapagliflozin	Biconvex, diamond shape, green tablet 10 mg (Size: 11 mm)	Bristol-Myers Squibb
Glimeperide	Flat-faced, oblong tablet, with notched sides at the bisect, pink tablet 1 mg	Sanofi Aventis

Table 4 Additional Drug

Treatment	Dosage form and strength	Manufacturer
Metformin	Film coated, white to off-white round tablet 1000 mg	Merck

7.2 Dose and treatment regimens

The investigational product, dapagliflozin or glimepiride, and additional drug, metformin 1000 mg will be taken orally.

Subjects to be allocated to the glimerpiride group will start taking 1mg glimepiride at visit 2. At visit 3, 4, 5 and 6, glimepiride can be up titrated to 2 mg to maintain glycemic control at the discretion of the investigator after evaluation of glycaemic control in subjects. Glimepiride can be down titrated to mitigate recurrent hypoglycaemic events at the discretion of the investigator but 0mg is not allowed. If further hypoglycaemic events occur with meeting the discontinuation criteria after taking the 1mg glimepiride, subjects may be discontinued from investigational product.

Dapagliflozin or glimepiride should be taken once daily, in the morning, as instructed by the investigator, immediately before or together with a meal.

The investigational product should be taken at approximately the same time of the day during the study period. The metformin should be taken just before or together with a meal according to the investigator's instruction.

Subjects should be instructed to abstain from all food and beverages for 12 hours prior to each clinical visit; however, drinking water after midnight is allowed. In the morning prior to each visit, acceptable concomitant medications can be taken with water only.

7.3 Labelling

IP for the study will be provided in commercially available packages with a study-specific label. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

7.6 Accountability

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

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

AZ or its representative will oversee that study personnel account for IPs received at the study center, unused IP and IP for appropriate destruction. At the termination of the Clinical Study or at the request of AZ, the Investigator will either return any unused IP to AZ, or destroy investigational product at the site depending on local regulations. If the IP is destroyed at site, the site personnel will account for all unused IP and for appropriate destruction. If the IP is

returned to AZ, the study site personnel or the AZ monitor will account for all received IP and return all unused IP to AZ. Certificates of delivery and return should be signed.

7.7 Concomitant and other treatments

7.7.1 General Medication

Other medication than described in Exclusion Criteria Section 3.2, Discontinuation Criteria

Section 3.9, and Prohibited Medication Section 7.7.2, which are considered necessary for the subject's safety and well-being (eg, to treat illnesses or complaints that occur during the study), may be given at the discretion of the investigator.

7.7.2 Prohibited Medication

Once enrolled, subjects must not receive any of the following for the duration of the study:

- Antihyperglycaemic medication other than protocol required medication (investigational product, open-label metformin, and when necessary open-label marketed sitagliptin).
- Insulin use for up to 14 days total during the study and up to 7 continuous days is permitted only in cases where:
- Subjects are unable to take oral medication (for example during a gastrointestinal illness)
- There is a documented illness or infection that requires additional therapy for maintaining glycaemic control
- Subjects have to temporarily stop investigational product and/or open-label metformin due to requirements of this clinical study protocol.

Also, insulin use for up to 7 days during hospitalization is allowed as long as the primary reason for hospitalization is not management of the subject's glycaemic control.

- Treatment with any systemic corticosteroid therapy that will involve >7 days of therapy (two temporary periods of higher daily doses (equivalent to oral prednisolone >10 mg/day) but no longer than 7 days each are allowed). The AstraZeneca representative should be consulted prior to beginning therapy with corticosteroids for subjects who require systemic corticosteroid treatment.
- Treatment with any medication that could have an influence on bone metabolism
- Any anti-obesity medication
- Hormone replacement therapy (not including local treatment)

- Administration of sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylpropion, methamphetamine, and/or phendimetrazine.

7.8 Post Study Access to Study Treatment

Study treatment is commercially available in Korea.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.

- Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject randomized and any subsequent amendments will be documented.

8.2 Sample size estimate

Redacted

Redacted [redacted]

Redacted [redacted]

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

Full Analysis Set (FAS)

The full analysis set will included all randomized subjects who receive at least one dose of study medication during the 52 week treatment period who have a non-missing baseline value and at least one post-baseline value for primary efficacy variable.

Whenever appropriate, missing values will be replaced by the last observation carried forward (LOCF) approach.

Whenever using the FAS, subjects will be presented in the treatment group to which they were randomized.

Per-Protocol Set (PPS)

The per-protocol set is a subset of the full analysis set consisting of subjects who do not violate the terms of the protocol, which may affect the efficacy endpoints significantly. All decisions to exclude subjects from the full analysis set to create the per-protocol set will be made prior to DB locking.

8.3.2 Safety analysis set

Safety analysis set will include all randomized subjects who received at least one dose of study medication during treatment period. Subjects who were dispensed the wrong randomized treatment will be counted in the treatment group for which they received medication.

8.3.3 PK analysis set

Not applicable.

8.3.4 PRO analysis set

Not applicable.

8.4 Outcome measures for analyses

Efficacy Variables

- Change from Baseline: Change from baseline will be calculated as absolute difference between the values measured at a specific time point after baseline minus baseline value. Baseline value is defined to be Visit 2 (randomization).

- Proportion of subjects achieving a glycemic response, defined as HbA1c<7.0% at Week 52.

If no measurements is available at Week 52, the last post-baseline HbA1c prior to Week 52 will be used instead for analysis.

Safety Variables

The following safety data will be collected: CBC, electrolytes, lipid, urinalysis, vital signs (pulse), reported hypoglycemic events and adverse events.

Change from screening (Visit 1) to each post-treatment time point where scheduled assessments were made will be calculated for CBC, electrolytes, lipid, and vital signs (pulse).

8.5 Methods for statistical analyses

8.5.1 Analysis of the primary variable (s)

The primary efficacy variable of the study is the change in total body fat mass from baseline using DXA scan in 52 weeks after the start of the treatment.

The null hypothesis H0 given below will be tested against the alternative hypothesis HA (α=0.05, two-sided). The alternative hypothesis states that the difference between two treatment groups in the mean change from Baseline to Week 52 is not zero:

$$H0: \mu T-\mu C=0 \qquad \text{versus} \qquad HA: \mu T-\mu C\neq 0$$

where μT denotes the mean change in total body fat mass from Baseline to Week 52 in the group of patients treated with Dapagliflozin (active investigational product, T) and μC the mean change in total body fat mass from Baseline to Week 52 in the group of patients with Glimepiride (comparator, C).

The change from Baseline to Week 52 in total body fat mass will be analysed using ANCOVA model with treatment group as factor and Baseline total body fat mass as a covariate. The model will be used to derive a least squares estimate of the treatment difference in mean change with corresponding two-sided 95% confidence interval (CI) and two-sided p-

value. Further, two-sided 95% CIs for the mean change within each treatment group will be calculated.

8.5.2 Analysis of the secondary variable(s)

The statistical significance levels for secondary endpoints will not be adjusted for multiple hypothesis testing and will be interpreted only descriptively

Change in HbA1c Levels from Baseline to 52 Weeks
Change from baseline to each visit measurement for HbA1c will be analyzed by a MMRM) method. All non-missing visit data will be used. The model will include terms for treatment group, visit, visit*treatment group and baseline measurement as a covariate. The model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided p-value. Missing data will not be imputed.

Change in Body Weight, Waist Circumference, BMI from Baseline to 52 Weeks
For change in body weight, waist circumference, BMI from baseline to 52 weeks, a same manner of secondary efficacy variable (HbA1c) will be performed.

Change in SBP and DBP from Baseline to 52 Weeks
For change in SBP and DBP from baseline to 52 week, a same manner of secondary efficacy variable (HbA1c) will be performed.

The Proportion of Subjects Achieving a Glycemic Response, Defined as HbA1c<7.0% at Week 52
The proportion of subjects who achieved an HbA1c<7.0 at week 52 (LOCF) will be assessed using logistic regression analysis with treatment group as a factor and baseline HbA1c as a covariate.
The number and percentage of responders and non-responders will be also presented. The odds ratio and its 95% CI from logistic regression will be estimated.

Change in FBS Levels from Baseline to 52 Weeks
For change in FBS from baseline to 52 week, a same manner of secondary efficacy variable (HbA1c) will be performed.

Change in Abdominal VAT and SAT Volume, VAT/SAT Ratio Using Abdominal CT from Baseline
For change in abdominal VAT and SAT volume, VAT/SAT ratio using abdominal CT from baseline to 52 week, a same manner of primary efficacy variable will be performed.

Changes in lean mass from baseline using Dual Energy X-ray Absorptiometry (DXA) scan from baseline to 52 weeks)
For changes in lean mass from baseline using Dual Energy X-ray Absorptiometry (DXA) scan, a same manner of primary efficacy variable will be performed.

Change in hsCRP and Adiponectin from baseline to 52 Weeks

For change in hsCRP and adiponectin from baseline to 52 week, a same manner of primary efficacy variable will be performed.

Safety Analysis
All safety analysis will be based on safety analysis set.

Change in CBC, Electrolytes, Lipid, Urinalysis from Baseline to 52 Weeks
Changes from baseline to 52 weeks for each clinical laboratory test, including CBC, electrolytes, and lipid measurements will be summarized using descriptive statistics by treatment group. In addition, the number and percent of patients with a marked abnormality in clinical laboratory tests including CBC, electrolytes, lipid and urinalysis will be summarized by treatment group.
Differences between treatment groups will be interpreted in a descriptive manner.

Number, Frequency and Proportion of Subjects Exposed to Adverse Events
The focus of adverse event reporting in result tables will be on TEAEs.
The number and percent of patients with adverse events, leading to discontinuation of IP, serious adverse events and adverse drug reactions will be summarized by system organ class (SOC) and preferred term for (PT) each treatment group using terms coded by MedDRA.
No statistical test will be performed to compare adverse event rates between treatment groups.
Serious adverse events will be listed in detail.

Number, Frequency and Proportion of Subjects Exposed to Hypoglycemic Events
Subjects reporting at least one episode of a hypoglycemic event will be summarized by counts, proportions, and corresponding 95% confidence intervals. A comparison between the treatment groups will be performed using two-sided Fisher's exact test.

8.5.3 Subgroup analysis

Not applicable.

8.5.4 Interim analysis

No interim analyses are planned.

8.5.5 Sensitivity analysis

Sensitivity analysis of the primary variable will be carried out and will be specified in the SAP.

8.5.6 Exploratory analysis

Not applicable.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 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 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).

9.2 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 study drug 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 (e.g., 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.

9.2.1 Source data

Original patient data in study sites

9.2.2 Study agreements

The Principal Investigator at each/the centre should 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 should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 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 is expected to start in Q4 2015 and to end by Q2 2017

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.

9.4 Data management by delegate of AstraZeneca

Data management will be performed by CRO, according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by CRO.

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

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. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process

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.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational database.

Data Management of genotype data

Not applicable.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 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.

10.2 Subject data protection

The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation.

- Study data will be stored in a computer database, maintaining confidentiality in accordance with relevant data protection and privacy legislation
- Patient data will be maintaining confidentiality in accordance with relevant data protection and privacy legislation
- For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an IRB may require direct access to parts of the hospital or practice source 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)

10.3 Ethics and regulatory review

An Institutional Review Board (IRB) 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 Investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

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

The IRB 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.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide Regulatory Authorities, IRB and Principal Investigators with safety updates/reports according to local requirements.

10.4 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.

The environment where the process of consent is conducted should be determined by the type of research being conducted but there should always be a period where a private, confidential, and "safe" setting is afforded to facilitate a constructive dialogue between the prospective subject and the person(s) involved in obtaining consent.

10.5 Changes to the protocol and informed consent form

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

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

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRB see Section 10.3.

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

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

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.

11. LIST OF REFERENCES

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Appendix A 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.

- 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

When making an assessment of causality consider the following factors 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?

- De-challenge 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.

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

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

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

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

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

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

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