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**Clinical Study Protocol**

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Date	5 February 2018

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**DAPACARD**

**A double-blind, randomized, parallel group, Phase IV study to investigate the effects of DAPAgliflozin on CARDiac substrate uptake, myocardial efficiency and myocardial contractile work in type 2 diabetes patients**

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**Sponsor:** AstraZeneca AB, S-151 85 Södertälje, Sweden

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## VERSION HISTORY

<b>Version 1, 25 October 2017</b>
Initial creation
<b>Version 2, 5 February 2018</b>
<p>Additional scanner type (integrated MRI/PET machine) for assessment of PET related endpoints.</p> <p>Rational for change: To provide the possibility to use several machines to optimize PET assessment availability.</p> <p>Sections affected: <a href="#">1.1</a> (Schedule of Activities), <a href="#">2.3</a> (Benefit/risk assessment), <a href="#">5.2</a> (Exclusion criteria), <a href="#">5.3</a> (Lifestyle restrictions), <a href="#">7.1.2</a> (Procedures for discontinuation of study treatment), <a href="#">8.1.2</a> (Cardiac Assessment via Computed Tomography and Positron Emission Tomography (CT-PET)).</p> <p>---</p> <p>Update regarding PET assessment with 18F-FTHA tracer. The 18F-FTHA examinations are exploratory and will not be performed in all the randomized patients. Instead, a minimum 40 and maximum of 44 of the randomized patients will perform the examinations.</p> <p>Rational for change: The change is due to ethical reasons and aims to limit unnecessary exposure to radioactivity.</p> <p>Sections affected: <a href="#">2.3</a> (Benefit/risk assessment), <a href="#">3</a> (Objectives and endpoints), <a href="#">8.1.2</a> (Cardiac Assessment via Computed Tomography and Positron Emission Tomography (CT-PET)), <a href="#">9.2</a> (Sample size determination), <a href="#">10</a> (References).</p>

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.

## TABLE OF CONTENTS

	TITLE PAGE.....	1
	VERSION HISTORY .....	2
	TABLE OF CONTENTS .....	3
<b>1.</b>	<b>PROTOCOL SUMMARY .....</b>	<b>7</b>
<b>1.1</b>	<b>Schedule of Activities (SoA).....</b>	<b>7</b>
<b>1.2</b>	<b>Synopsis .....</b>	<b>9</b>
<b>1.3</b>	<b>Schema .....</b>	<b>11</b>
<b>2.</b>	<b>INTRODUCTION .....</b>	<b>12</b>
<b>2.1</b>	<b>Study rationale .....</b>	<b>12</b>
<b>2.2</b>	<b>Background.....</b>	<b>12</b>
2.2.1	Cardiovascular disease in type 2 diabetes mellitus.....	12
2.2.2	Cardiovascular outcomes with SGLT-2 inhibition.....	12
<b>2.3</b>	<b>Benefit/risk assessment .....</b>	<b>13</b>
<b>3.</b>	<b>OBJECTIVES AND ENDPOINTS .....</b>	<b>14</b>
<b>4.</b>	<b>STUDY DESIGN.....</b>	<b>16</b>
<b>4.1</b>	<b>Overall design.....</b>	<b>16</b>
<b>4.2</b>	<b>Scientific rationale for study design .....</b>	<b>16</b>
<b>4.3</b>	<b>Justification for dose .....</b>	<b>18</b>
<b>4.4</b>	<b>End of study definition.....</b>	<b>18</b>
<b>5.</b>	<b>STUDY POPULATION .....</b>	<b>18</b>
<b>5.1</b>	<b>Inclusion criteria .....</b>	<b>18</b>
<b>5.2</b>	<b>Exclusion criteria .....</b>	<b>19</b>
<b>5.3</b>	<b>Lifestyle restrictions.....</b>	<b>21</b>
5.3.1	Meals and dietary restrictions.....	21
5.3.2	Caffeine, alcohol, and tobacco.....	21
5.3.3	Activity.....	21
<b>5.4</b>	<b>Screen failures .....</b>	<b>21</b>
<b>6.</b>	<b>STUDY TREATMENTS .....</b>	<b>21</b>
<b>6.1</b>	<b>Treatments administered .....</b>	<b>22</b>
6.1.1	Investigational products .....	22
6.1.2	Non-Investigational Medicinal Products.....	22
<b>6.2</b>	<b>Preparation/handling/storage/accountability .....</b>	<b>22</b>
<b>6.3</b>	<b>Measures to minimise bias: randomisation and blinding.....</b>	<b>23</b>
<b>6.4</b>	<b>Treatment compliance .....</b>	<b>24</b>

<b>6.5</b>	Concomitant therapy .....	24
6.5.1	Background medication.....	24
6.5.2	Other concomitant treatment .....	25
<b>6.6</b>	Dose modification (Not applicable).....	25
<b>6.7</b>	Treatment after the end of the study (Not applicable) .....	25
<b>7.</b>	<b>DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL .....</b>	<b>25</b>
<b>7.1</b>	Discontinuation of study treatment.....	25
7.1.1	Temporary discontinuation (Not applicable).....	26
7.1.2	Procedures for discontinuation of study treatment .....	26
<b>7.2</b>	Lost to follow-up .....	26
<b>7.3</b>	Withdrawal from the study.....	27
<b>8.</b>	<b>STUDY ASSESSMENTS AND PROCEDURES.....</b>	<b>27</b>
<b>8.1</b>	Efficacy assessments.....	28
8.1.1	Cardiac Assessment via Magnetic Resonance Imaging (MRI) .....	28
8.1.2	Cardiac Assessment via Computed Tomography and Positron Emission Tomography (CT-PET) or via Magnetic Resonance Imaging and Positron Emission Tomography (MRI-PET) .....	29
<b>8.2</b>	Safety assessments .....	31
8.2.1	Clinical safety laboratory assessments.....	31
8.2.2	Physical examinations.....	32
8.2.3	Vital signs.....	32
8.2.4	Electrocardiograms .....	32
8.2.5	Echocardiograms .....	33
8.2.6	Other safety assessments.....	33
8.2.6.1	Diabetic ketoacidosis .....	33
<b>8.3</b>	Collection of adverse events.....	33
8.3.1	Method of detecting AEs and SAEs .....	34
8.3.2	Time period and frequency for collecting AE and SAE information .....	34
8.3.3	Follow-up of AEs and SAEs .....	34
8.3.4	Adverse event data collection.....	35
8.3.5	Causality collection.....	35
8.3.6	Adverse events based on signs and symptoms .....	36
8.3.7	Adverse events based on examinations and tests .....	36
<b>8.4</b>	Safety reporting and medical management .....	36
8.4.1	Reporting of serious adverse events .....	36
8.4.2	Pregnancy .....	37
8.4.2.1	Maternal exposure.....	37
8.4.3	Overdose.....	38
8.4.4	Medication error .....	38
<b>8.5</b>	Pharmacokinetics .....	38

8.5.1	Determination of drug concentration .....	39
8.5.2	Storage and destruction of pharmacokinetic samples .....	39
<b>8.6</b>	<b>Pharmacodynamics .....</b>	<b>39</b>
<b>8.7</b>	<b>Genetics .....</b>	<b>39</b>
<b>8.8</b>	<b>Biomarkers .....</b>	<b>39</b>
8.8.1	Storage, re-use and destruction of biomarker samples .....	41
<b>8.9</b>	<b>Medical Resource Utilization and Health Economics .....</b>	<b>41</b>
<b>9.</b>	<b>STATISTICAL CONSIDERATIONS .....</b>	<b>41</b>
<b>9.1</b>	<b>Statistical hypotheses .....</b>	<b>41</b>
<b>9.2</b>	<b>Sample size determination.....</b>	<b>41</b>
<b>9.3</b>	<b>Populations for analyses.....</b>	<b>42</b>
<b>9.4</b>	<b>Statistical analyses .....</b>	<b>43</b>
9.4.1	Efficacy analyses .....	43
9.4.2	Safety analyses.....	44
9.4.3	Other analyses.....	44
9.4.4	Methods for multiplicity control.....	44
<b>9.5</b>	<b>Interim analyses (Not applicable) .....</b>	<b>44</b>
9.5.1	Data monitoring committee (DMC) (Not applicable).....	44
<b>10.</b>	<b>REFERENCES .....</b>	<b>44</b>
<b>11.</b>	<b>SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS .....</b>	<b>48</b>

## LIST OF TABLES

Table 1	Study of Assessments .....	7
Table 2	Study Objectives .....	14
Table 3	Study Treatments .....	22
Table 4	Restricted medications .....	24
Table 5	Prohibited medications .....	24
Table 6	MRI variables.....	29
Table 7	CT-PET or MRI-PET variables .....	31
Table 8	Laboratory safety variables.....	32
Table 9	Biomarkers.....	40

## LIST OF FIGURES

Figure 1	Study design.....	11
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## LIST OF APPENDICES

<b>Appendix A</b>	Regulatory, ethical and study oversight considerations .....	48
<b>Appendix B</b>	Adverse event definitions and additional safety information .....	52
<b>Appendix C</b>	Handling of Human Biological Samples .....	56
<b>Appendix D</b>	Abbreviations .....	58

## 1. PROTOCOL SUMMARY

### 1.1 Schedule of Activities (SoA)

**Table 1 Study of Assessments**

Visit Day	Screening 1 -21 to 0	Randomization Baseline 2 1	Interim visit (Phone visit) 3 14	End of treatment 4 42	Safety Follow-up (Phone visit) 5 49	Details in protocol section or Appendix Visit 2 and 4 may be conducted over two days
<b>Informed consent</b>						
	X					Section 5.1
<b>Inclusion / exclusion criteria</b>						
	X	X				Section 5.1 and 5.2
<b>Routine clinical procedures</b>						
<b>Demography</b>						
	X					Section 5.1
<b>Physical examination</b>						
	X					Section 8.2.2
<b>Medical history and comorbid conditions</b>						
	X	X		X		Section 5.1 Section 8.2.3
<b>Vital signs</b>						
	X					Section 8.2.2
<b>Height</b>						
	X	X		X		Section 8.2.2 Section 8.2.4
<b>Weight</b>						
	X					Section 8.2.5
<b>ECG</b>						
	X					Section 6.5
<b>Echocardiogram</b>						
	X	X	X	X		
<b>Concomitant medication</b>						
	X					
<b>Routine safety measurements</b>						
<b>SAE</b>						
	X	X	X	X	X	Section 8.3
<b>DAE</b>						
		X	X	X	X	Section 8.3
<b>Diabetic ketoacidosis events</b>						
		X	X	X	X	Section 8.2.6.1
<b>Pregnancy test (serum or urine)</b>						
	X	X		X		Section 5.2, 8.1.2 and Table 8
<b>Clinical chemistry and haematology</b>						
	X	X		X		Section 8.2.1
<b>Blood and Urine analyses (except Safety analyses)</b>						
<b>HbA1c (screening)</b>						
	X					Section 5.1
<b>Biomarkers (fasting)</b>						
		X		X		Section 8.5, 8.8 and Table 9

**Table 1 Study of Assessments**

Visit Day	Screening	Randomization Baseline	Interim visit (Phone visit)	End of treatment	Safety Follow-up (Phone visit)	Details in protocol section or Appendix
	1	2	3	4	5	Visit 2 and 4 may be conducted over two days
	-21 to 0	1	14	42	49	
(visit window $\pm$ 4 days from Day 14 onwards)						
Urine sample		X		X		Section 8.8
<b>Pharmacokinetic measurements</b>						
Pre-dose blood sample				X		Section 8.5
<b>Efficacy measurements</b>						
MRI (fasting)		X		X		Section 8.1.1 and 5.3
CT-PET/MRI-PET (fasting)		X		X		Section 8.1.2 and 5.3
<b>Study Treatment Administration</b>						
Randomisation		X				Section 6.3
Study treatment dispensed (daily dosing)		X				Section 6
Study treatment return				X		Section 6.4



## 1.2 Synopsis

### National Coordinating Investigator, Sweden

PPD

SWEDEN

### National Coordinating Investigator, Finland

PPD

FINLAND

### Co-coordinating Investigator, Sweden

PPD

PPD

SWEDEN

**Protocol Title:** A double-blind, randomized, parallel group, Phase IV study to investigate the effects of DAPAgliflozin on CARDiac substrate uptake, myocardial efficiency and myocardial contractile work in type 2 diabetes patients

### Short Title: DAPACARD

#### Rationale:

The sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin was associated with lower cardiovascular mortality and hospitalization for heart failure. The effect was apparent within months from treatment start, suggesting that mechanisms beyond improved glucose control may be involved. Additionally, the SGLT2 inhibitor canagliflozin reduced combined endpoint of cardiovascular death and disease, including hospitalization for heart failure further reinforcing that SGLT2 inhibitors protect the heart in type 2 diabetes. The aim of the current study is to investigate the effects of dapagliflozin (a SGLT2i) on myocardial function and metabolism.

#### Objectives and Endpoints

Primary objective:	Endpoint/variable:
To compare the changes in <b>global longitudinal strain of the left ventricle (GLSLV)</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Change from baseline in <b>GLSLV (%)</b>
Secondary objective:	Endpoint/variable:
To compare the changes in <b>myocardial efficiency (%)</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Change from baseline in <b>myocardial efficiency (%)</b>
Safety objective:	Endpoint/variable:

## Objectives and Endpoints

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To evaluate the safety and tolerability of dapagliflozin.	Adverse Events leading to Discontinuation of Study Medication (DAEs) / Serious Adverse Events (SAEs) Collection of clinical chemistry/haematology parameters
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### Overall design:

A double-blind, randomized, parallel group placebo controlled Phase IV study in type 2 diabetes patients.

Planned number of sites: approximately 3-4

Participating countries: 2, Sweden and Finland

### Study Period:

Estimated date of first patient enrolled Q1 2018

Estimated date of last patient completed Q3 2019

### Number of Subjects:

Planned number of subjects: 52 (26 per arm) randomized subjects, assuming a 15% non-evaluable rate. The evaluable population is the Per Protocol population.

It is estimated that approximately 80-100 subjects need to be screened. Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently randomly assigned to Study treatment.

### Treatments and treatment duration:

The study includes 5 visits; screening, randomization/baseline, interim, end-of-treatment and follow-up during a total period of maximum 74 days for each subject.

After a screening period of up to 21 days, subjects will be randomized in a 1:1 ratio to dapagliflozin 10 mg or placebo tablet, taken orally once daily. The treatment period is 6 weeks after which a follow-up contact is made approximately 7 days later.

### Statistical methods

The analysis of efficacy will be based on the evaluable analysis set. Change from baseline values for the primary variable, global longitudinal strain of left-ventricle, will be analyzed using analysis of covariance. The model will include terms for baseline value and treatment.

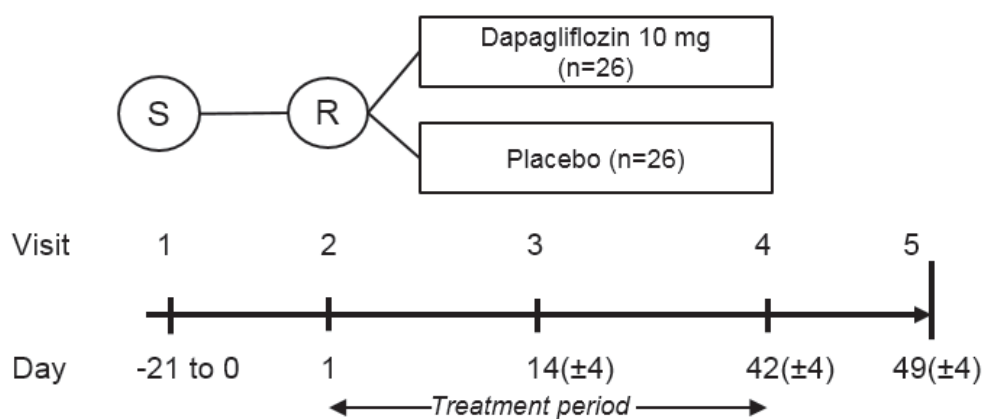
Least square mean change from baseline estimates, as well as the corresponding 95 percent confidence limits, will be generated from the fitted model for each treatment group. The difference in least square mean between the dapagliflozin and placebo treatment groups, the corresponding 95 percent confidence interval and the p-value will also be presented. Statistical significance will be inferred at a (two-sided) 0.05 level.

The analysis of safety will be based on the safety analysis data set. Safety data during the treatment period will be evaluated and variables will only be summarized descriptively. Discontinuation due to adverse events and serious adverse events will be summarized by system organ class and preferred term and listed for each patient. The number and percent of subjects that discontinue due to adverse events and, separately, that experience at least one serious adverse event will be summarized for each treatment group. Descriptive statistics of continuous measurements (e.g. safety laboratory assessments and vital signs) will be presented by treatment for both absolute values and changes from baseline. Safety laboratory, vital signs, physical examination and ECG findings will be listed by patient.

### 1.3 Schema

The general study design is summarised in [Figure 1](#).

**Figure 1** Study design



S = Screening, R = Randomization 1:1

## **2. INTRODUCTION**

### **2.1 Study rationale**

The sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin was associated with lower cardiovascular (CV) mortality and hospitalization for heart failure in the EMPA-REG study (Zinman et al 2015). The effect was apparent within months from treatment start, suggesting that mechanisms beyond improved glucose control may be involved. Additionally, the SGLT2 inhibitor canagliflozin reduced combined endpoint of CV death and disease, including hospitalization for heart failure in the recently presented CANVAS study (Neal et al 2017) further reinforcing that SGLT2 inhibitors protect the heart in Type 2 diabetes (T2D) patients.

The aim of the current study is to investigate the effects of dapagliflozin (a SGLT2i) on myocardial function and metabolism.

### **2.2 Background**

#### **2.2.1 Cardiovascular disease in type 2 diabetes mellitus**

Worldwide, CV disease is the leading cause of death in patients with diabetes and make up approximately 50 % of deaths in patients with T2D (WHO 2016). Although improved glycaemic control in patients with diabetes reduces the risk of microvascular complications (Holman et al 2008, Lampa 2015, UKPDS-Group 1998), evidence that glucose lowering leads to reduced cardiovascular events and death is sparse (Holman et al 2014). The results of the 10 year post-trial follow up of the UK Prospective Diabetes Study suggested a long-term modest effect on myocardial infarction or on all-cause mortality (Holman et al 2008). On the other hand, results from ACCORD, ADVANCE, and VADT did not show that intense glucose-lowering in T2D patients lowered the CV risk (Holman et al 2014).

#### **2.2.2 Cardiovascular outcomes with SGLT-2 inhibition**

There are a number of potential mechanisms that could help to explain the CV benefits reported in the EMPA-REG and CANVAS studies (Neal et al 2017, Zinman et al 2015). SGLT2 inhibition leads to increased urinary excretion of glucose and sodium and thus increased diuresis. As a consequence of SGLT2 inhibition, a decrease in Hemoglobin A1c (HbA1c), body weight, and blood pressure and an increase in hematocrit (Hct) is observed. However, none of these effects is believed to fully explain the reported CV benefits. Mechanistic studies are therefore warranted to elucidate potential SGLT2i beneficial effects on the cardiovascular system (Ferrannini 2017). A complementary hypothesis is based on the increased urinary glucose excretion by dapagliflozin, which will lead to enhanced night-time catabolism, followed by increased glycogenolysis, gluconeogenesis and production of ketone bodies. The increased gluconeogenesis during night-time would inhibit mammalian Target Of Rapamycin (mTOR), which would increase autophagy/mitophagy of damaged mitochondria and biogenesis as well as fusion of mitochondria maximizing bioenergetic efficiency (Rambold et al 2015), hence supporting myocardial health.

A detailed description of the chemistry, pharmacology, efficacy, and safety of dapagliflozin is provided in the Investigator's Brochure (IB).

### **2.3 Benefit/risk assessment**

Dapagliflozin has global market approval and based on global cumulative sales figures up to March 2016, it is estimated that dapagliflozin has been administered during >1 000 000 patient years and approved in more than 85 countries. Details regarding potential risks associated with administration of dapagliflozin once a day are provided in the IB.

Due to its mode of action resulting in increased urinary glucose excretion, an increased risk of urinary tract infections and genital infections has been seen. Based on the mechanism of action of dapagliflozin there may be a potential risk for this compound to cause hypovolaemia or electrolyte imbalance. As a precaution, patients who, in the judgment of the Investigator, may be at risk for dehydration or volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, will be carefully monitored for their volume status. Note that in this study use of loop diuretics is considered an exclusion criteria. In patients already receiving dapagliflozin who develop conditions that may cause hypovolaemia or electrolyte imbalance, decisions to interrupt or discontinue dapagliflozin therapy and management of patients will be based on clinical judgment.

After the introduction of dapagliflozin and other SGLT2 inhibitors, there have been post marketing reports of ketoacidosis, including diabetic ketoacidosis (DKA), in patients with Type 1 diabetes (T1D) and T2D, although a causal relationship has not been established. Patients presenting signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, will be assessed for ketoacidosis, even if blood glucose levels are < 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation of Study treatment should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., T1D, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse.

The CT-PET and MRI-PET examinations involve ionizing radiation. Each PET scanning with [11C]-Acetate (400 MBq) and [18F]-6-thia-heptadecanoic acid ([18F]-FTHA) (150 MBq) causes a calculated radiation burden of 1.4 and 3.15 mSv, respectively, to each subject.

The total PET radiation burden for subjects undergoing two scans with both [11C]-Acetate and [18F]-FTHA will be 9.1 mSv. The total PET radiation burden for subjects only undergoing two scans of [11C]-Acetate will be 2.8 mSv.

The attenuation localization CT examinations associated with the CT-PET examinations will give a summarized dose of 0.8 mSv. The attenuation MRI examination associated with the MRI-PET examinations is not associated with any radioactive dose.

The total absorbed dose from all CT-PET or MRI-PET examinations for individuals enrolled in this study will therefore be less than 10mSv, which is within the annual limits for medical radiation exposure (ICRP 2007).

Considering the non-clinical and clinical experience with dapagliflozin and the precautions included in the study protocol, participation in this study should present a minimal and thus acceptable risk to patients who meet the inclusion/exclusion criteria and consent to take part in the study.

### 3. OBJECTIVES AND ENDPOINTS

**Table 2 Study Objectives**

<i>Primary Objective:</i>	<i>Endpoint/Variable:</i>
To compare the changes in <b>global longitudinal strain of the left ventricle (GLSLV)</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Change from baseline in <b>GLSLV (%)</b>
<i>Secondary Objective:</i> To compare the changes in <b>myocardial efficiency (%)</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	<i>Endpoint/Variable:</i> Change from baseline in <b>myocardial efficiency (%)</b>
<i>Safety Objective:</i> To evaluate the safety and tolerability of dapagliflozin.	<i>Endpoint/Variable:</i> Adverse Events leading to Discontinuation of Study Medication (DAEs) / Serious Adverse Events (SAEs) Collection of clinical chemistry/haematology parameters
<i>Exploratory Objective:</i> To compare the changes in <b>wash-out in the myocardium of [<sup>11</sup>C]-Acetate (Kmono, 1/min)</b> achieved with dapagliflozin vs. placebo after 6 weeks of double-blind treatment.	<i>Endpoint/Variable:</i> Changes from baseline in <b>wash-out in the myocardium of [<sup>11</sup>C]-Acetate (Kmono)</b>
To compare the changes in <b>myocardial perfusion (ml/min/g) measured by [<sup>11</sup>C]-Acetate</b> achieved with dapagliflozin vs. placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>myocardial perfusion measured by [<sup>11</sup>C]-Acetate</b>
To compare the changes in <b>wash-out of [<sup>11</sup>C]-Acetate (Kmono, 1/min) in relation to myocardial perfusion (K1, ml/min/g)</b> achieved with dapagliflozin vs. placebo after 6 weeks of double-blind treatment.	Change from baseline in <b>wash-out of [<sup>11</sup>C]-Acetate (Kmono) in relation to myocardial perfusion (K1)</b>
To compare the changes in <b>myocardial fatty acid uptake (MFAU, μmol/min/g) by [<sup>18</sup>F]-FTHA</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>myocardial fatty acid uptake by [<sup>18</sup>F]-FTHA</b>
To compare the changes in <b>fatty acid uptake in liver (μmol/min/g) by [<sup>18</sup>F]-FTHA</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>fatty acid uptake in liver by [<sup>18</sup>F]-FTHA</b>

**Table 2 Study Objectives**

To compare the changes in <b>fatty acid uptake in kidney cortex (<math>\mu\text{mol}/\text{min}/\text{g}</math>) by [18F]-FTHA</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment	Changes from baseline in <b>fatty acid uptake in kidney cortex by [18F]-FTHA</b>
To compare the changes in <b>fatty acid uptake in brain (<math>\mu\text{mol}/\text{min}/\text{g}</math>) by [18F]-FTHA</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>fatty acid uptake in brain by [18F]-FTHA</b>
To compare the changes in <b>Left Ventricular (LV) global radial strain and LV global circumferential strain</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>LV global radial strain (%) and LV global circumferential strain (%)</b>
To compare the changes in <b>LV global systolic longitudinal strain rate, LV global diastolic longitudinal strain rate, LV global diastolic radial strain rate, LV global systolic radial strain rate, LV global diastolic circumferential strain rate and LV global systolic circumferential strain rate</b> , achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>LV global systolic longitudinal strain rate (<math>\%s^{-1}</math>), LV global diastolic longitudinal strain rate (<math>\%s^{-1}</math>), LV global diastolic radial strain rate (<math>\%s^{-1}</math>), LV global systolic radial strain rate (<math>\%s^{-1}</math>), LV global diastolic circumferential strain rate (<math>\%s^{-1}</math>) and LV global systolic circumferential strain rate (<math>\%s^{-1}</math>)</b>
To compare the changes in <b>LV end-diastolic volume (mL), LV end-systolic volume (mL), and LV stroke volume (mL)</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>LV end-diastolic volume (mL), LV end-systolic volume (mL), and LV stroke volume (mL)</b>
To compare the changes in <b>LV mass (g), LV mass/end-diastolic volume (g/mL) and LV ejection fraction (%)</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>LV mass (g), LV mass/end-diastolic volume (g/mL) and LV ejection fraction (%)</b>
To compare the changes in <b>Left atrial volume (min, max) (mL), Left atrial ejection fraction (%) and transmitral flow velocity indices (E/A (1), E (cm/s), A (cm/s) and DT (ms))</b> , achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>Left atrial min volume (mL), Left atrial max volume (mL), Left atrial ejection fraction (%) and transmitral flow velocity indices (E/A (1), E (cm/s), A (cm/s) and DT (ms))</b>
To compare the changes in <b>blood biomarkers (e.g. HbA1c, Hematocrit, Hb, FGF-21, NT-proBNP)</b> achieved with dapagliflozin vs. placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>blood biomarkers (e.g. HbA1c, Hematocrit, Hb, FGF-21, NT-proBNP)</b>
To compare the changes from baseline in <b>body weight, and blood pressure</b> achieved with dapagliflozin versus placebo after 6 weeks of double-blind treatment.	Changes from baseline in <b>body weight, as well as systolic and diastolic blood pressure</b>
To explore <b>associations between change in GLSLV and change in myocardial efficiency as well as associations to changes in other exploratory endpoints</b> with potential importance.	Change from baseline in <b>GLSLV</b> and change from baseline in <b>myocardial efficiency</b> , as well as changes in <b>other endpoints as defined above</b>

**Table 2 Study Objectives**

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To evaluate the <b>pharmacokinetics</b> of dapagliflozin by a	Plasma <b>concentrations of dapagliflozin</b> in a sample at
single pre-dose sample at end of study.	end of study (pre-dose)

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## 4. STUDY DESIGN

### 4.1 Overall design

This is a randomised, placebo-controlled, double-blind, parallel-group, international, multicentre, Phase IV study to investigate the effects of dapagliflozin on cardiac substrate uptake, myocardial efficiency and myocardial contractile work in T2D patients. Eligible subjects with T2D before randomisation and fulfilling all of the inclusion criteria and none of the exclusion criteria will be randomised in a 1:1 ratio to dapagliflozin 10 mg or placebo once daily and treated for six weeks. The study includes five visits.

For an overview of the study design, see [Figure 1](#), Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

### 4.2 Scientific rationale for study design

The study is investigating early changes in the heart metabolism and function. The reason for this is the rapid effects on CV risk and especially risk for heart failure hospitalization reported in the EMPA-REG and CANVAS studies ([Ferrannini 2017](#), [Ferrannini et al 2016](#), [Neal et al 2017](#), [Zinman et al 2015](#)). The study is therefore designed to mainly assess changes in the heart that could be ascribed to changed metabolism and fluid balance, and not effects secondary to structural changes/re-modelling of the heart.

In this study, we will investigate the effects of dapagliflozin (a SGLT2i) on myocardial metabolism and function. Energy metabolism in the heart includes several components such as micro- and macrovascular circulation, substrate utilization, oxidative phosphorylation and production of Adenosine triphosphate (ATP) taking place in the mitochondria ([Neubauer 2007](#)). We will also investigate myocardial perfusion, substrate utilization and measures of energy status of the heart including myocardial energy efficiency and strain as a surrogate for myofibril contractile work.

The primary end-point is GLSLV (Global Longitudinal Left Ventricular Strain) measured with Magnetic Resonance Imaging (MRI). GLSLV is a marker of myofibril contractile work, which is dependent on ATP production. Changed ATP production can occur as a result of changed perfusion or altered mitochondrial function in the heart. Moreover, GLSLV has been associated with relevant clinical endpoints. GLSLV was the best predictor of future CV events in a Heart Failure with preserved Ejection Fraction (HFpEF) population ([Shah et al 2015](#)). Moreover, optimisation of glucose control, blood pressure, and lipids of T2D patients with poor glycemic control for 12 months has been shown to improve GLSLV ([Leung et al 2016](#)).



Preliminary findings from an in-house study investigating the effects of dapagliflozin on monkeys with metabolic syndrome and no diabetes indicated improvements of different measures of longitudinal strain of the heart after 5 weeks of treatment.

The secondary endpoint is myocardial efficiency (%). The myocardial efficiency calculation is based on an estimate of energy used for producing LV contractile work (mean arterial pressure (MAP) x stroke volume (SV) x heart rate (HR) / myocardial mass) compared to the total cardiac work which is calculated based on the total myocardial oxygen consumption per myocardial mass (Tuunanen et al 2006). The myocardial oxygen consumption is directly proportional to the clearance of [11C]-Acetate. [11C]-Acetate is immediately converted into [11C]-Acetyl CoA in the cell and after entering the citric acid cycle the label 11C is released as 11C-CO<sub>2</sub>. Therefore it is assumed that the myocardial monoexponential washout of [11C]-Acetate is a marker of the citric cycle activity and hence mitochondrial function. This tracer has been used in multiple studies of oxidative metabolism (Lindner et al 2016, Nesterov et al 2015, Tuunanen et al 2006, Tuunanen et al 2007). Moreover, initial uptake of [11C]-Acetate in the heart will be used to estimate myocardial perfusion (van den Hoff et al 2001). Myocardial perfusion will be investigated as an exploratory end-point.

Patients with T2D seems to have impaired myocardial metabolism both in the fasting state and during insulin infusion. Interestingly, insulin infusion resulted in increased heart work and reduced myocardial efficiency (Mather et al 2016). Moreover, T2D patients with no evidence of coronary artery disease or impaired cardiac function have reduced cardiac energy metabolism as indicated by lower PCr/ATP ratio as compared to healthy volunteers (Scheuermann-Freestone et al 2003). The PCr/ATP ratio was negatively correlated with fasting plasma free fatty acid (FFA) levels, suggesting a negative effect of higher FFA levels on cardiac energy metabolism. Thus, insulin, which lowers plasma free fatty acids increase cardiac work and reduce myocardial efficiency, but higher levels of FFA is associated with reduced myocardial energy reserve (PCr/ATP) indicating a complex relationship between myocardial energy state and substrate uptake in T2D that is not fully understood.

A key exploratory endpoint in the study is the difference in uptake of FFA in the myocardium by dapagliflozin versus placebo measured by a fatty acid PET-ligand, [<sup>18</sup>F]-FTHA. This tracer has been used in several intervention and non-intervention studies of myocardial metabolism previously (Labbé et al 2012, Labbé et al 2014, Tuunanen et al 2007). It is hypothesized that FFA uptake will increase more with dapagliflozin than with placebo treatment in the planned experimental situation (≥6 hour fast). Since there are reasons to believe that dapagliflozin treatment also results in different exposure to FFA in other tissues, the brain, liver and kidney will be investigated with respect to FFA uptake.

Plasma/serum samples obtained in the study will either be assessed directly such as FGF-21 and NT-proBNP or stored in a biobank for potential future analysis of blood biomarkers to further explore the mechanisms behind the effects of SGLT2i on myocardial metabolism.

In summary, the primary aim of the DAPACARD study is to investigate the effects of dapagliflozin on GLSLV and the secondary aim is to investigate the effects of dapagliflozin on myocardial efficiency. These effects will be associated with other potential effects of dapagliflozin which could impact heart metabolism and function such as FFA uptake, changes

in plasma substrates (glucose, free fatty acids and beta-hydroxybutyrate), hemoglobin (Hb)/hematocrit, and heart perfusion.

### **4.3 Justification for dose**

Dapagliflozin (Forxiga<sup>®</sup>) will be given at the dose of 10 mg per day. That is the dose of Forxiga<sup>®</sup> that is approved in Sweden and Finland for treatment of T2D. The treatment duration is 6 weeks and chosen to be able to detect changes in myocardial metabolism that would influence heart function. The comparator is placebo since the study duration is relatively short and use of placebo allow specific conclusions regarding the effects of dapagliflozin.

### **4.4 End of study definition**

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

A subject is considered to have completed the study when he/she has completed his/her last scheduled visit or last scheduled procedure shown in the Schedule of Activities (SoA).

See Appendix A 6 for guidelines for the dissemination of study results.

## **5. STUDY POPULATION**

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol, “enrolled” subjects are defined as those who sign informed consent. “Randomized” subjects are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled subjects see Section 7.3.

### **5.1 Inclusion criteria**

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses. The ICF process is described in Appendix A 3.
3. Females or males  $\geq 40$  years up to 75 years of age.
4. Individuals with type 2 diabetes diagnosed for at least 6 months based on the American Diabetes Association standards (ADA 2017) and on stable dose of metformin for at least 6 weeks prior to screening and HbA1c at screening visit of  $\geq 42$  mmol/mol (6.0%) and  $\leq 75$  mmol/mol (9.0%) measured at local hospital laboratory.
5. No significant signs or symptoms of coronary artery disease or, if known coronary artery disease, currently free of symptoms and a) all major epicardial vessels with  $< 50\%$  stenosis within 12 months prior to screening, or b) if revascularized with all major epicardial vessels with  $< 50\%$  remaining stenosis after stenting or bypass surgery procedure determined between 3 and 12 months prior to screening.
6. Normal left ventricular ejection fraction ( $\geq 50\%$ ) assessed within 1 year prior to informed consent, and if applicable, after most recent acute episode of coronary artery syndrome, or at screening visit.
7. Body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>.

## 5.2 Exclusion criteria

### Medical conditions

1. Blood pressure at screening that would require a change in blood pressure treatment over the study period or any of the following: systolic blood pressure  $> 160$  mmHg or diastolic blood pressure  $> 100$  mmHg.
2. History of stroke or other clinically significant cerebrovascular disease.
3. Any of the following cardiovascular diseases known within 3 months prior to signing the consent at enrolment:
  - a. Atrial fibrillation, or other unstable or severe arrhythmia affecting heart function
  - b. Unstable heart failure or any heart failure with NYHA class III and IV
  - c. Significant valvular disease
  - d. Significant peripheral artery disease
4. Planned cardiac surgery or angioplasty within 3 months from enrolment.
5. Clinical diagnosis of type 1 diabetes, maturity onset diabetes of the young (MODY), secondary diabetes or diabetes insipidus.
6. Verified body weight variability of  $> 3$  kg during the 3 preceding months before screening.
7. Active malignancy requiring treatment at the time of visit 1 (with the exception of successfully treated basal cell or treated squamous cell carcinoma).

8. Patients with severe hepatic impairment (Child-Pugh class C).
9. Unstable or rapidly progressing renal disease.
10. Clinically significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.

**Prior/concomitant therapy**

11. Ongoing treatment with other antidiabetic drugs than metformin.
12. Ongoing treatment with loop diuretics.
13. Ongoing weight-loss diet (hypocaloric diet) or use of weight loss agents.
14. Contraindications to dapagliflozin therapy.
15. Ongoing treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except for T2D.

**Prior/concurrent clinical study experience**

16. Previous enrolment in the present study or participation in another clinical study with an investigational product during the last 1 month prior to screening.

**Diagnostic assessments**

17. Estimated Glomerular Filtration Rate (eGFR) <45 mL/min/1.73 m<sup>2</sup>, based on the MDRD study equation ([www.kidney.org/content/mdrd-study-equation](http://www.kidney.org/content/mdrd-study-equation)) (eGFR = 175 x (SCr)<sup>-1.154</sup> x (age)<sup>-0.203</sup> x 0.742 [if female] x 1.212 [if Black]).
18. Alcohol or drug abuse within the 3 months prior to informed consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to study procedures or study treatment intake.
19. Any condition when MRI and CT-PET or MRI-PET is contraindicated such as, but not limited to, having a metallic implant (such as pacemaker or cochlear implant), permanent make up, claustrophobia or BMI ≥40 kg/m<sup>2</sup>).

**Other exclusions**

20. Involvement in the planning and/or conduct of the study (applies to AstraZeneca, UCR and/or Antaros staff and/or staff at the study site).
21. Plasma donation within one month of screening or any blood donation/blood loss >450 mL during the 3 months prior to screening.
22. Women who has a positive pregnancy test at enrolment or randomization, or are breastfeeding.

## **5.3 Lifestyle restrictions**

### **5.3.1 Meals and dietary restrictions**

Biomarker samples will be obtained after an overnight fast of 9 hours  $\pm$ 1 hour in the morning, as according to Schedule of Activities (SoA). The information will be captured in the Case Report Form (CRF).

MRI and CT-PET or MRI-PET to be conducted after an overnight fast in the morning or  $\geq$ 6 hours fasting period, at the same time for each individual at the visits as according to SoA. The information will be captured in the CRF.

### **5.3.2 Caffeine, alcohol, and tobacco**

Subjects are instructed to abstain from products containing nicotine, alcohol and caffeine for  $\geq$ 6 hours prior to MRI and CT-PET or MRI-PET examinations. Information and deviations are captured in the CRF.

### **5.3.3 Activity**

Subjects should be encouraged not to change their lifestyle during study participation including exercise, eating and drinking habits.

## **5.4 Screen failures**

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently randomly assigned to Study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

In case of HbA1c, creatinine or other safety values ([Table 8](#)) are out of range and considered not clinically significant, retesting will be allowed within the screening visit period, at the Investigators discretion.

## **6. STUDY TREATMENTS**

Study treatment in this study refers to dapagliflozin or placebo.

## 6.1 Treatments administered

### 6.1.1 Investigational products

**Table 3 Study Treatments**

	<i>Treatment 1</i>	<i>Treatment 2</i>
<b>Study treatment name:</b>	Dapagliflozin	Placebo
<b>Dosage formulation:</b>	Plain, green, diamond-shaped, film-coated tablet; 10 mg	Plain, green, diamond-shaped, film-coated tablet
<b>Route of administration</b>	Oral	Oral
<b>Dosing instructions:</b>	One tablet to be taken, once daily, in the morning (except of onsite visits days with fasting blood samples collection, when tablet needs to be taken afterwards)	One tablet to be taken, once daily, in the morning (except of onsite visits days with fasting blood samples collection, when tablet needs to be taken afterwards)
<b>Packaging and labelling</b>	Study treatment will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study treatment will be provided in bottles. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.

### 6.1.2 Non-Investigational Medicinal Products

During the study the Non Investigational Medicinal Products (NIMP) will be sourced from a third part vendor at each PET facility and used during the study related procedures to assess end-points. All NIMPs will be stored, prepared, administered and handled by the site according to standard practice. See the Imaging charter and Core-lab manual for further information.

NIMPs in this study are [11C]-Acetate and [18F]-FTHA. GMP grade unlabelled precursors and reference standards for the NIMPs will be sourced by each imaging site from a third-party vendor. The precursors for [11C]-Acetate and [18F]-FTHA are radiolabelled locally with Carbon-11 and Fluorine-18, respectively, at each imaging site according to documented GMP procedures just prior the PET examinations.

## 6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the site agreement.

### **6.3 Measures to minimise bias: randomisation and blinding**

All subjects will be centrally assigned to randomised study treatment using a telephone service (Call Centre). Before the study is initiated, the telephone number and call-in directions for the Call Centre, as well as log-in information and a User Manual for the Call Centre will be provided to each site.

If a subject withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

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<b>Blinded study using Call Centre</b>	<p>The Call Centre will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Routines for this will be described in the Call Centre user manual that will be provided to each centre.</p> <p>The randomisation code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.</p> <p>AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.</p> <p>Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.</p>
<b>Blind Break (via Call Centre)</b>	<p>The Call Centre will be provided with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the subject's best interest for the investigator to know the study treatment assignment. The sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition (e.g. antidote available). In this case, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF (electronic or paper), as applicable. Study unblinding should not occur until database lock and all decisions on the evaluability of the data from each individual subject have been made and documented.</p>

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Personnel performing the pharmacokinetic (PK) analysis of dapagliflozin concentration will be provided the randomization code to identify patients on active drug and will therefore be unblinded. See Section 8.5.

## 6.4 Treatment compliance

Any change from the dosing schedule as well as dose discontinuations should be recorded in the CRF.

Subjects should return all unused study treatment, as well as empty bottles, as according to the SoA. If a subject discontinues study treatment prematurely all study medication should be returned at the earliest opportunity.

The Investigator or delegate is responsible for managing the study treatment from receipt by the study site until the destruction or return of all unused study treatment from the subjects.

## 6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

### Table 4 Restricted medications

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In general, all concomitant medications should be kept stable throughout the study. Most important medication to keep at stable dose from 6 weeks before screen and during the study are metformin, thyroid hormones, thiazides, beta-blockers, mineralcorticoid antagonists, ARBs and ACE inhibitors (affecting glucose, plasma volume and heart function).

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### Table 5 Prohibited medications

<i>Prohibited medication/class of drug:</i>	<i>Indication:</i>
<u>Other anti-diabetic treatments than metformin</u> including: other SGLT2i, insulin, glitazones, pramlinitide, DPP-IV inhibitors, GLP-1 analogues and sulfonylurea	For treatment of T2D
<u>Loop-diuretics</u> such as furosemide	For treatment of fluid retention

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#### 6.5.1 Background medication

Subjects must be on a stable dose of metformin for at least 6 weeks prior to screening and throughout the study.



### **6.5.2 Other concomitant treatment**

Other medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

### **6.6 Dose modification (Not applicable)**

### **6.7 Treatment after the end of the study (Not applicable)**

## **7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL**

### **7.1 Discontinuation of study treatment**

Subjects may be discontinued from study treatment in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- SAE that, in the opinion of the Investigator contraindicated further dosing of study treatment.
- Severe non-compliance with the Clinical Study Protocol.
- Safety reasons as judged by the Investigator or by the sponsor.
- Positive pregnancy test (discontinue study treatment and notify AZ representative).
- Subjects should be discontinued from study medication if they experience severe hypoglycaemia as defined by the American Diabetes Association (ADA):
  - Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions.

Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose level.

- Acute renal insufficiency or worsened chronic renal insufficiency based on repeat eGFR values (eGFR<45 mL/minute/1.73m<sup>2</sup>). The re-test should be scheduled within 4 days, whenever possible.
- A decrease in renal function that would preclude continued treatment with metformin according to local guidance.
- If ketoacidosis is suspected, discontinuation of study medication should be considered and the patient should be promptly evaluated.

- Patients should be discontinued from study treatment if the initial and repeat laboratory tests meet any of the following criteria:
  - ALT and/or AST are  $>3$  x ULN and total bilirubin  $>2$  x ULN
  - ALT and/or AST are  $>5$  x ULN for  $\geq 14$  consecutive days, at any time after initial confirmatory results
  - ALT and /or AST are  $> 8$  x ULN

Reason for discontinuation of study medication, safety assessments and potential DAE/SAEs should be collected if possible. Collection of efficacy data could be decided in collaboration between the Investigator and the Sponsor, depending duration of study treatment.

#### **7.1.1 Temporary discontinuation (Not applicable)**

#### **7.1.2 Procedures for discontinuation of study treatment**

The investigator should instruct the subject to contact the site before or at the time if Study treatment is stopped. A subject that decides to discontinue Study treatment will always be asked about the reason(s) and the presence of any SAEs/DAEs. The date of last intake of Study treatment should be documented in the CRF. All Study treatment should be returned by the subject at their next on-site study visit or unscheduled visit. Subjects permanently discontinuing Study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

Discontinuation of Study treatment, for any reason, does not impact on the subject's participation in the study. The subject should continue attending subsequent study visits and data collection should continue according to the study protocol. If the subject does not agree to continue in-person study visits, a modified follow-up should be arranged if possible to collect safety information and endpoints. This could be a telephone contact with the subject, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A subject that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Collection of endpoints (primarily MRI and CT-PET or MRI-PET) should be decided in collaboration between the Investigator and the Sponsor.

## **7.2 Lost to follow-up**

A subject will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.

- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject or next of kin by e.g. repeat telephone calls, certified letter to the subject's last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.
- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study the subject should be considered to be lost to follow up with unknown vital status at end of study and censored at latest follow up contact.

### **7.3 Withdrawal from the study**

A subject may withdraw from the study (e.g. withdraw consent), at any time (investigational product **and** assessments) at his/her own request, without prejudice to further treatment.

A subject who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g. telephone contact, a contact with a relative or treating physician, or information from medical records).

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any SAEs/DAEs. The Investigator will follow up subjects as medically indicated.

It should be decided in collaboration between the Investigator and the Sponsor what follow-up need to be completed for each discontinued subject. All Study treatment should be returned by the subject.

## **8. STUDY ASSESSMENTS AND PROCEDURES**

Study procedures and their timing are summarised in the Schedule of Activities (SoA).

The investigator will ensure that data are recorded on the electronic Case Report Forms (CRF). The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic CRFs. A copy of the completed electronic CRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue Study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g. echocardiography) and obtained before signing of the ICF and recorded in the medical records may be utilised for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 220 mL. However, repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## **8.1 Efficacy assessments**

### **8.1.1 Cardiac Assessment via Magnetic Resonance Imaging (MRI)**

Planned time points for Magnetic Resonance Imaging (MRI) assessments are provided in the SoA.

The patient will undergo MRI scanning in order to assess cardiac function and morphology, refer to [Table 6](#) for variables. The MRI scanning will be made after fasting for at least 6 hours and at the same time of day at both visits. Time of examination and fasting period should be captured in the CRF to ensure that the time of examinations will be same at following visit.

The cardiac MRI examination will be performed in accordance with a pre-defined MRI protocol, with the total scan time at each visit estimated to 45 minutes. Images from all sites will be analyzed in a blinded fashion at the Antaros Medical core-lab in Uppsala using a dedicated software package and certified analysts.

A clinical radiologic assessment of all acquired MRI images will be performed by a local radiologist. The assessment will be reported to the Investigator at the referring site, who will review and file the assessment in the subject's source documents. If clinically significant findings are noted the Investigator should evaluate and handle the finding as per standard medical/clinical judgement.

Prior to study start, MRI scan protocols will be setup at the respective imaging sites in accordance to an imaging manual.

**Table 6 MRI variables**

<i>Variables:</i>	<i>Unit:</i>
<i>GLSLV</i>	<i>%</i>
<i>LV global radial strain</i>	<i>%</i>
<i>LV global circumferential strain</i>	<i>%</i>
<i>LV global diastolic longitudinal strain rate</i>	<i>s<sup>-1</sup></i>
<i>LV global systolic longitudinal strain rate</i>	<i>s<sup>-1</sup></i>
<i>LV global diastolic radial strain rate</i>	<i>s<sup>-1</sup></i>
<i>LV global systolic radial strain rate</i>	<i>s<sup>-1</sup></i>
<i>LV global diastolic circumferential strain rate</i>	<i>s<sup>-1</sup></i>
<i>LV global systolic circumferential strain rate</i>	<i>s<sup>-1</sup></i>
<i>LV end-diastolic volume</i>	<i>mL</i>
<i>LV end-systolic volume</i>	<i>mL</i>
<i>LV stroke volume</i>	<i>mL</i>
<i>LV mass</i>	<i>g</i>
<i>LV mass/end-diastolic volume</i>	<i>g/mL</i>
<i>LVEF</i>	<i>%</i>
<i>Left atrial min volume</i>	<i>mL</i>
<i>Left atrial max volume</i>	<i>mL</i>
<i>Left atrial ejection fraction</i>	<i>%</i>
<i>E/A</i>	<i>1</i>
<i>E</i>	<i>cm/s</i>
<i>A</i>	<i>cm/s</i>
<i>DT</i>	<i>ms</i>

### 8.1.2 Cardiac Assessment via Computed Tomography and Positron Emission Tomography (CT-PET) or via Magnetic Resonance Imaging and Positron Emission Tomography (MRI-PET)

Planned time points for Computed Tomography and Positron Emission Tomography (CT-PET) or Magnetic Resonance Imaging and Positron Emission Tomography (MRI-PET) assessments are provided in the SoA. The CT-PET or MRI-PET assessments can be performed on the same day as the MRI assessment if logistically possible, or on separate days.

The subject will undergo CT-PET or MRI-PET scanning to assess myocardial metabolism, and, for subjects also undergoing 18F-FTHA CT-PET or MRI-PET scanning, fatty acid metabolism in myocardium, brain, liver and kidney cortex will be assessed as well (see [Table 7](#) for variables). Importantly, subjects will do either MRI-PET or CT-PET, and will do the same kind of methodology both at baseline and end-of study. The CT-PET or MRI-PET scanning will be made after a fast as well as abstinence from nicotine, alcohol and caffeine for at least 6 hours and at the same time of day at both visits. A pregnancy test is performed

before any PET radioligand administration (applicable if it is unclear to any extent if the woman is post-menopausal or not). Time of examination, result of pregnancy test, fasting period and any deviations from nicotine, alcohol and caffeine abstinence should be captured in the CRF to ensure that the time of examinations will be same at following visit. Heart rate and blood pressure is measured and recorded for input to the 11C-Acetate measurement but will not be entered into the CRF.

A cardiac 11C-Acetate CT-PET or MRI-PET examination is performed (IV 400 MBq 11C-Acetate) on all randomised subjects. For this examination no blood sampling is performed. If the 18F-FTHA examination is performed on the same visit, the subject will rest for at least 60 minutes while the 11C radioactivity decays before the 18F-FTHA examination.

A cardiac 18F-FTHA CT-PET or MRI-PET examination is performed (IV 150 MBq 18F-FTHA) on minimum 40 and maximum 44 randomised subjects. This is due to ethical reasons and aims to limit unnecessary exposure to radioactivity. A power calculation was performed using the variability of fatty acid measurements in a healthy population (Viljanen et al 2009) and what is regarded as a clinically meaningful effect, indicating that about 40 patients is sufficient to reach approximately 80-90% power. The subject is further examined by CT-PET or MRI-PET over the liver, kidney cortex and brain (in this order) for uptake of 18F-FTHA. Arterialized venous samples are acquired throughout to assess P-NEFA and 18F-FTHA metabolism by metabolite analysis (total blood volume taken <25mL per examination). In case 18F-FTHA metabolite analysis data is incomplete (too few points to estimate a mono-exponential curve) or missing due to technical issues, a population mean estimate from the study population (baseline or follow up subpopulation) will be used instead.

The 11C-acetate and 18F-FTHA CT-PET or MRI-PET examination may be performed on the same day or on separate visits. The duration of the 11C-Acetate visit at the PET facility is estimated to 1h (of which 0.5 h in the CT-PET or MRI-PET scanner). The duration of the 18F-FTHA visit at the CT-PET or MRI-PET facility is estimated to 1.5 h (of which 1h in the CT-PET or MRI-PET scanner).

A clinical radiologic assessment of acquired 11C-Acetate CT-PET or MRI-PET images will be performed by a local radiologist. The assessment will be reported to the Investigator at the referring site, who will review and file the assessment in the subject's source documents. If clinically significant findings are noted the Investigator should evaluate and handle the finding as per standard medical/clinical judgement.

Images from all sites will be analyzed in a blinded fashion at the Antaros Medical core-lab in Uppsala using a dedicated software package and certified analysts.

A test CT-PET or MRI-PET examination with a cylindrical test phantom filled with Fluorine-18 will be performed at each site as part of the site initiation routine to ascertain that the correct scan protocols are in place.

**Table 7 CT-PET or MRI-PET variables**

<i>Variables:</i>	<i>Unit:</i>	<b>11C-Acetate</b>	<b>18F-FTHA</b>
<i>Myocardial Efficiency</i>	%	X	
<i>Myocardial Kmono</i>	l/min	X	
<i>Myocardial Kmono / Myocardial perfusion</i>	-	X	
<i>Myocardial perfusion</i>	mL/min/g	X	
<i>Myocardial Fatty Acid Uptake*</i>	μmol/g/min		X
<i>Liver Fatty Acid Uptake*</i>	μmol/g/min		X
<i>Kidney cortex Fatty Acid Uptake *</i>	μmol/g/min		X
<i>Brain Fatty Acid Uptake *</i>	μmol/g/min		X

\* Not applicable for subjects only performing 11C-Acetate.

## 8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

### 8.2.1 Clinical safety laboratory assessments

See [Table 8](#) for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see [Section 8.3.7](#).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values and units) will be recorded on the appropriate CRF.

The clinical chemistry and haematology will be performed at a local laboratory. Urine dipstick will be analysed at the study centre.

**Table 8 Laboratory safety variables**

<i>Haematology/Haemostasis (whole blood)</i>	<i>Clinical Chemistry (serum or plasma)</i>
<i>B-Haemoglobin (Hb)*</i>	<i>S-Creatinine</i>
<i>B-Hematocrit*</i>	<i>S-Bilirubin, total</i>
	<i>S-Alkaline phosphatase (ALP)</i>
	<i>S-Aspartate transaminase (AST)</i>
	<i>S-Alanine transaminase (ALT)</i>
	<i>P-Glucose</i>
<i>Urinalysis (dipstick)</i>	
<i>Pregnancy test (Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L), dipstick analysed at the study centre)**</i>	<i>S/P-βHCG (if urine pregnancy dipstick result is positive)</i>

\* B-Hb and B-Haematocrit also serves as efficacy variables

\*\* Applicable to women if it is unclear to any extent if the woman is post-menopausal or not

### 8.2.2 Physical examinations

A physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen and volume status.

Physical examination will be performed at timelines as specified in the SoA, Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as adverse events, see Section 8.3.7 for details.

Body weight will be assessed as specified in the SoA; in the morning, after a visit to the lavatory, in underwear/light clothing. With exception for the screening visit, body weight should be assessed after an overnight fast. For a single individual, all weight assessments should be made using the same calibrated scale.

Height will be assessed only at screening.

### 8.2.3 Vital signs

Pulse rate and blood pressure will be assessed at timelines as specified in the SoA. Two measurements will be taken with at least 5 minutes of rest prior to and between measurements, in a quiet setting without distractions, in a sitting position and before any blood collection. The same arm for blood pressure assessment will be used throughout the study. Information regarding the measurement will be recorded in the CRF.

### 8.2.4 Electrocardiograms

Single resting 12-lead ECG will be obtained for screening purpose using an ECG machine. The ECG reading should be evaluated by the Investigator and recorded in the CRF as normal, abnormal, not clinically significant or clinically significant.



### **8.2.5 Echocardiograms**

Echocardiogram will be obtained only at screening and assessed for normal left ventricular ejection fraction ( $\geq 50\%$ ) only if not available within 1 year prior to informed consent and, if applicable, after most recent acute episode of coronary artery syndrome. Information regarding the measurement will be recorded in the CRF.

Normal left ventricular ejection fraction is part of eligibility criteria.

### **8.2.6 Other safety assessments**

#### **8.2.6.1 Diabetic ketoacidosis**

Subjects on Study treatment who present signs and symptoms consistent with Ketoacidosis (DKA), including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation of Study Treatment should be considered and the subject should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse. As dapagliflozin should be used with caution in these subjects it has been taken in consideration in the eligibility criteria.

#### **Potential events of Diabetic Ketoacidosis**

All potential events of DKA will be recorded in the CRF and submitted to an independent DKA Adjudication Committee. The DKA Committee T2D will assess available information on each potential DKA event and will classify the event in accordance with the definitions in the DKA Adjudication Charter T2D.

The DKA Adjudication Committee will be kept blinded to the study treatment received by each subject with a potential DKA event in the clinical study. A separate DKA Adjudication Manual will define and describe the procedures for the collection of DKA information, handling, adjudication criteria and reporting of these events/cases.

### **8.3 Collection of adverse events**

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

The definitions of AE/SAE can be found in [Appendix B](#). **In this study**, collection of AE data is limited to collection of Serious Adverse Events (SAE) and Adverse Events leading to Discontinuation of Study Medication (DAE). In addition, all possible events (non-serious, SAE, DAE) of diabetic ketoacidosis are to be collected.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see Section 8.3.3.

### **8.3.1 Method of detecting AEs and SAEs**

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

### **8.3.2 Time period and frequency for collecting AE and SAE information**

SAE data will be collected from time of signature of informed consent (screening) throughout the treatment period including the follow-up period.

DAE data will be collected from the first intake of study treatment, throughout the treatment period.

Diabetic ketoacidosis events will be collected from the first intake of study treatment throughout the treatment period and including the follow-up period.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in [Appendix B](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in [Appendix B](#).

### **8.3.3 Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAE/DAE/Diabetic ketoacidosis events, will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

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

#### **8.3.4 Adverse event data collection**

The following variables will be collect for each SAE/DAE event;

- 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(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused subject'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 to other medication'

#### **8.3.5 Causality collection**

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

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

A guide to the interpretation of the causality question is found in [Appendix B](#).

### 8.3.6 Adverse events based on signs and symptoms

**In this study**, collection of AE data is limited to collection of SAE and DAE. In addition, all possible events (non-serious, SAE, DAE) of diabetic ketoacidosis are to be collected.

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

### 8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should 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 (DAE).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment that fulfil criteria for SAE/DAE will be reported.

## 8.4 Safety reporting and medical management

### 8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product/study treatment, or to the study procedure(s). All SAEs will be reported via a specific SAE form and also recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day 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 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 i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Investigators or other site personnel send the SAE form by fax to the designated AstraZeneca representative.

For further guidance on the definition of a SAE, see [Appendix B](#).

## 8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca, via a specific pregnancy form, except for:

- If the pregnancy is discovered before the study subject has received any study treatment
- Pregnancies in the partner of male subjects

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

### 8.4.2.1 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 1 day 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 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

### 8.4.3 Overdose

Dapagliflozin has been well tolerated at doses of up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and patients with T2D. Suspected single intake of more than 50 tablets of 10 mg dapagliflozin tablets or repeated intake of more than 10 tablets of 10 mg dapagliflozin tablets should be reported on the CRF overdose module. If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

- 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 treatment 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 8.3.2. For other overdoses, reporting must occur within 30 days.

### 8.4.4 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day 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 completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in [Appendix B](#).

## 8.5 Pharmacokinetics

Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of Study treatment as specified in the SoA. Instructions for the collection and handling of biological samples will be provided by the sponsor or analytical test site. The actual date and time (24-hour clock time) of the sample will be recorded.

Samples will be used to evaluate the PK of Study treatment. The sample will be divided into 2 aliquots (1 each for PK and a back-up).

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

#### **8.5.1 Determination of drug concentration**

Samples for determination of drug concentration will be analysed by analytical test sites on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

#### **8.5.2 Storage and destruction of pharmacokinetic samples**

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report (CSR).

### **8.6 Pharmacodynamics**

Pharmacodynamic parameters are an integrated part of the efficacy assessments of the study and are described in Section [8.1.1](#) and [8.1.2](#).

### **8.7 Genetics**

Genetic testing is not evaluated in this study.

### **8.8 Biomarkers**

Mandatory collection of samples for biomarker research is also part of this study. The following fasting blood and spot urine samples for biomarker research are required and will be collected from all subjects in this study as specified in the SoA:

**Table 9 Biomarkers**

<i>Source:</i>	<i>Analyte:</i>	<i>Comment:</i>	
<i>Fasting blood</i>	<i>Glucose</i>	<i>Serum sample taken for biomarker research. Samples also taken in association with PET (local lab)</i>	
	<i>HbA1c</i>		
	<i>NEFA</i>		
	<i>Beta-hydroxybutyrate</i>		
	<i>Lactate</i>		
	<i>Uric acid</i>		
	<i>Insulin</i>		<i>Two samples taken 15 minutes apart</i>
	<i>Glucagon</i>		
	<i>NT-proBNP</i>		
	<i>FGF-21</i>		
	<i>hsCRP</i>		
	<i>hsTroponin-I</i>		
	<i>Total cholesterol</i>		<i>Baseline (Visit 2) only</i>
	<i>Triglycerides</i>		<i>Baseline (Visit 2) only</i>
<i>HDL-C</i>	<i>Baseline (Visit 2) only</i>		
<i>Plasma and serum sample for biobank</i>	<i>Possible analyses after study end</i>		
<i>Urine</i>	<i>Glucose</i>	<i>To assess after database lock</i>	
	<i>Creatinine</i>		
	<i>Urine sample for biobank</i>	<i>Possible analyses after study end</i>	

All protocol-required laboratory assessments, as defined in [Table 9](#), must be conducted in accordance with the laboratory manual and the SoA.

Self-assessment of glucose is allowed, but not asked for nor captured in CRF.

Biomarkers, as specified in [Table 9](#), will be tested in Plasma, Serum and Urine for exploratory objectives to evaluate changes achieved with dapagliflozin compared to placebo after 6 weeks of treatment.

In addition, Plasma, Serum and Urine samples will be collected and analysis may be performed on biomarkers thought to play a role for dapagliflozin mechanism of action especially heart metabolism and function including, but not limited to, metabolic, cardiovascular and renal biomarkers to evaluate their association with observed clinical responses to dapagliflozin treatment.



### **8.8.1 Storage, re-use and destruction of biomarker samples**

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report (CSR) itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study treatment to generate hypotheses to be tested in future research.

## **8.9 Medical Resource Utilization and Health Economics**

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# **9. STATISTICAL CONSIDERATIONS**

## **9.1 Statistical hypotheses**

The primary null statistical hypothesis: The adjusted mean change in the **GLSLV** from baseline to the end of treatment for patients on dapagliflozin is equal to the corresponding change for patients on placebo.

The primary alternative statistical hypothesis: The adjusted mean change in **GLSLV** from baseline to the end of treatment for patients on dapagliflozin is not equal to the corresponding change for patients on placebo.

## **9.2 Sample size determination**

Change in GLSLV from baseline to the end of treatment has been selected as the primary endpoint in the DAPACARD study.

In patients with pre-existing cardiac abnormality (i.e. aortic stenosis or atherosclerosis) but without T2D, the average GLSLV at baseline is approximately -16.0% (Gjesdal et al 2016, Singh et al 2015). The common standard deviation in estimated change from baseline GLSLV is assumed to be 2.0%, which is a conservative approximation of the results found in the literature (1.73% in (Singh et al 2015), 1.3% in (Gjesdal et al 2016)). Average GLSLV in T2D subjects with prior MI at baseline is anticipated to be -11%. The estimated between-group difference in average improvement in GLSLV is anticipated to be -2%. It is estimated that 17 evaluable patients/arm provides 80% power at a two-sided alpha level of 0.05 to detect a treatment difference of 2% in the change from baseline in GLSLV between dapagliflozin and placebo, assuming a common standard deviation in estimated change from baseline in GLSLV of 2.0%. To accommodate the statistical testing of secondary endpoint, the number of evaluable patients/arm is increased to 22 (total of 44).

Change in myocardial efficiency from baseline to the end of treatment (%), measured as external LV work per gram (defined as MAP x SV x HR/ LV mass) divided by total LV work

per gram (linearly proportional to  $MVO_2$  in turn linearly proportional from  $[^{11}C]$ -Acetate clearance / LV mass) is the secondary endpoint in the DAPACARD study.

Tuunanen et al reported the healthy subjects baseline myocardial efficiency in two different studies to be 54.3 (N=36) and 49.3 (N=8) (pooled mean of 50.21)  $\text{mmHg} \cdot \text{L} \cdot \text{g}^{-1}$ , with a standard deviation (SD) of 8.9 and 14.2  $\text{mmHg} \cdot \text{L} \cdot \text{g}^{-1}$ , respectively (Tuunanen et al 2006, Tuunanen et al 2007). A 25% increase translates into 12.55 with a SD of 14.2  $\text{mmHg} \cdot \text{L} \cdot \text{g}^{-1}$  between dapagliflozin and placebo treatment group. Twenty two (22) evaluable subjects per group (total of 44) are needed to detect a treatment difference of 12.55, at a 2-sided significance level of 0.05 and 80% power. Assuming a 15% non-evaluable rate, total of 52 (26 per group) subjects will be randomized.

The  $^{18}F$ -FTHA examinations are exploratory and will not be performed in all the randomized patients. Instead, a minimum 40 and a maximum of 44 of the randomized patients will be scheduled for examination for  $^{18}F$ -FTHA uptake in heart, liver, kidney and the brain. This is due to ethical reasons and aims to limit unnecessary exposure to radioactivity. The authors in Viljanen et al (Viljanen et al 2009), report SD of myocardial fatty acid uptake to be 0.4 (before diet) and 0.2 (after diet) in a healthy population, leading to a pooled SD of 0.32. No information is available regarding the magnitude of the treatment effect in the planned study, but an effect of approximately 0.3-0.4 (approximately 10% relative change) is judged to be clinically relevant. Using this assumption, and the pooled estimate of the SD as a conservative approximation of the variability of measurement differences between baseline and end of treatment, leads to approximately 80-90% power with 40 randomized patients (at a two-sided alpha level 0.05 and assuming 15% non-evaluable rate).

### 9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
<i>Enrolled Analysis Set</i>	The Enrolled Analysis Set will consist of all subjects who signed informed consent.
<i>Randomized Analysis Set</i>	The Randomized Analysis Set will consist of all randomized subjects who received at least one dose of study medication during the treatment period. In analyses of the Randomized Subjects Dataset, subjects will be summarized by the treatment group to which they were randomized (even if the treatment they received is different).
<i>Evaluable Analysis Set</i>	The Evaluable Analysis Set will be the primary analysis dataset, and is a subset of the Randomized Analysis Set. This is also known as the Per-Protocol population. All data points after an important protocol deviation will be excluded from this analysis. Important protocol deviations are defined as deviations which could potentially affect the interpretability of the study results. The criteria for important protocol deviations will be defined in the statistical analysis plan. Subjects will be represented using the treatment group to which they were received.

<b>Population</b>	<b>Description</b>
<i>Safety Analysis Set</i>	The Safety Analysis Set will consist of all subjects who received at least one dose of study medication during the treatment period. Subjects will be presented by randomized treatment group, except if information indicates that a subject received a different treatment for the entire course of their participation in the treatment period. In this case, the safety data for such a subject will be presented by the treatment which they actually received.
<i>PK Analysis Set</i>	The PK analysis set will include subjects for whom PK data are evaluable (with no important protocol deviations thought to significantly affect the pharmacokinetics of the drug). PK data may be reported separately from the clinical study report.

## 9.4 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be developed and finalised before database lock and will describe in more detail the subject populations to be included in the analyses, as well as procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary and exploratory endpoints. Any deviations from this plan will be reported in the clinical study report.

### 9.4.1 Efficacy analyses

The analysis of efficacy will be based on the evaluable analysis set. Change from baseline values for the primary variable (GLSLV) will be analyzed using Analysis of Covariance (ANCOVA). The model will include terms for baseline value and treatment.

Least Square Mean (LSM) change from baseline estimates, as well as the corresponding 95 percent confidence limits, will be generated from the fitted model for each treatment group. The difference in LSM between the dapagliflozin and placebo treatment groups, the corresponding 95 percent confidence interval and the p-value will also be presented. Statistical significance will be inferred at a (two-sided) 0.05 level.

Analysis of secondary variable will be performed using the evaluable analysis set. ANCOVA, as described above for the primary analysis, will be used. Statistical significance will be inferred at a (two-sided) 0.05 level.

Analysis of exploratory variables will be performed using the evaluable analysis set. Analysis of the change from baseline endpoints will be performed using ANCOVA, as for the primary endpoint. Details of the statistical analysis of the other exploratory objectives, as well as procedures for handling of missing values, will be provided in the SAP.

#### **9.4.2 Safety analyses**

The analysis of safety will be based on the safety analysis set. All SAEs occurring from the time of signature of informed consent up to the follow-up period will be summarized by system organ class (SOC) and preferred term (PT). The number and percent of subjects that discontinue due to adverse events (DAE) and serious adverse event (SAE) will be summarized for each treatment group. Descriptive statistics of continuous measurements (e.g. safety laboratory assessments and vital signs) will be presented by treatment for both absolute values and changes from baseline. Safety laboratory, vital signs, physical examination and ECG findings will be listed by patient. Further details on planned safety analyses will be provided in SAP.

#### **9.4.3 Other analyses**

PK and biomarker exploratory analyses will be described in the statistical analysis plan. The population PK analysis will be described and presented separately from the main clinical study report (CSR).

#### **9.4.4 Methods for multiplicity control**

As the nature of the study is exploratory (based on hypotheses presented in Section 4.2, Scientific rationale of the study), with no confirmatory component, no control of family-wise error rate will be performed. However, due to the large number of considered endpoints, it is likely that several of them will be found to be “significant” as a consequence of the Type I error rate allowable by the hypothesis testing procedure, even if no effect is truly present. Thus, the interpretation of the findings will be done with care, keeping in mind both whether the detected patterns are clinically meaningful and the expected number of false discoveries that might occur due to chance.

### **9.5 Interim analyses (Not applicable)**

#### **9.5.1 Data monitoring committee (DMC) (Not applicable)**

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## **11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

### **Appendix A Regulatory, ethical and study oversight considerations**

#### **A 1 Regulatory and ethical considerations**

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

#### **A 2 Financial disclosure**

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.



### **A 3 Informed consent process**

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

The ICF will contain a separate section that addresses the use of samples for exploratory research. The investigator or authorised designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. 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 already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

### **A 4 Data protection**

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

### **A 5 Committees structure**

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

## **A 6 Dissemination of clinical study data**

A description of this clinical trial will be available on <http://astrazenecaclinicaltrials.com> and <http://www.clinicaltrials.gov> as will the summary of the main study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## **A 7 Data quality assurance**

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

## **A 8 Source documents**

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the Source Data Agreement for each site.

## **A 9 Publication policy**

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## **Appendix B Adverse event definitions and additional safety information**

**In this study**, collection of AE data is limited to collection of Serious Adverse Events (SAE) and Adverse Events leading to Discontinuation of Study Medication (DAE). In addition, all possible events (non-serious, SAE, DAE) of diabetic ketoacidosis are to be collected.

### **B 1 Definition of adverse events**

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

### **B 2 Definitions of serious adverse event**

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

### **B 3 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 (e.g., hepatitis that resolved without hepatic failure).

### **B 4 Hospitalisation**

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., 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.

## **B 5 Important medical event or medical treatment**

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 treatment 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 (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

## **B 6 Intensity rating scale:**

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 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 Appendix B 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 Appendix B 2.

## **B 7 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.

## **B 8 Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study treatment that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding Call centre errors)
- Wrong drug administered to participant (excluding Call centre errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from Call centre - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

## **Appendix C Handling of Human Biological Samples**

### **C 1 Chain of custody of biological samples**

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

The 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).

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 will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

### **C 2 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.

As collection of the biological sample(s) is an integral part of the study, then the subject is withdrawn from further study participation.

The 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 organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/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 organizations 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.



### C 3 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](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 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 e.g. 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 e.g. Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus 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](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 Abbreviations

<b>Abbreviation or special term</b>	<b>Explanation</b>
ACE	angiotensin converting enzyme
ADA	American diabetes association
AE	adverse event
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
ATP	adenosine triphosphate
BMI	body mass index
BP	blood pressure
CRF	case report form (electronic/paper)
CSA	clinical study agreement
CSR	clinical study report
CT	computed tomography
CV	cardiovascular
DAE	discontinuation of investigational product due to adverse event
DKA	diabetic ketoacidosis
EC	ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECG	electrocardiogram
EF	ejection fraction
eGFR	estimated glomerular filtration rate
FFA	free fatty acid
FTHA	[18F]-6-thia-heptadecanoic acid
GCP	Good Clinical Practice
GLSLV	global longitudinal strain of the left ventricle
GMP	Good Manufacturing Practice
HbA1c	hemoglobin A1c
HCG	Human chorionic gonadotropin
Hct	hematocrit
HFpEF	heart failure with preserved ejection fraction
HR	heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

<b>Abbreviation or special term</b>	<b>Explanation</b>
International Coordinating 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.
LSLV	last subject last visit
LSM	least square mean
LV	left ventricular
MAP	mean arterial pressure
MDRD study equation	modification for diet in renal disease study equation, for estimating eGFR with standardized serum creatinine values
MFAU	myocardial fatty acid uptake
MI	myocardial infarction
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NEFA	Non-esterified (“free”) Fatty Acid
NIMP	non-investigational medicinal product
OAE	other significant adverse event
PET	positron emission tomography
PI	principal investigator
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGLT2i	sodium-glucose cotransporter 2 inhibitor
SoA	Schedule of Activities
SOC	system organ class
SUV	standardised uptake value
SV	stroke volume
TIA	transient ischemic attack
T1D	type 1 diabetes
T2D	type 2 diabetes
UCR	Uppsala Clinical Research center
WBDC	web based data capture