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THE EFFECT OF DAPAGLIFLOZIN ON INFLAMMATION AND ENDOTHELIAL DYSFUCTION

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
T2DM	Type 2 Diabetes Mellitus
NFkB	Nuclear factor kappaB

1. INTRODUCTION

The insulin-resistant state of type 2 diabetes mellitus (T2DM) is largely mediated by inflammatory pathways affecting skeletal muscle (1, 2), which is the primary site of whole body insulin resistance (3). Nuclear factor kappa B (NFkB) regulates pro-inflammatory cytokines which ultimately impair skeletal muscle insulin signaling and fatty acid oxidation; its activity reflects overall inflammatory tone in skeletal muscle (2, 4). Recent human studies confirm that NFkB is elevated in the skeletal muscle of T2DM human subjects (5-7). Furthermore, the same inflammatory processes and signaling impairments contribute to worsening endothelial dysfunction (8), which is an independent predictor for future cardiovascular events in T2DM (9).

In the present study we will assess whether dapagliflozin reduces monocyte inflammation and improves endothelial dysfunction in patients with type 2 diabetes.

1.1 Background

Multiple rodent models of T2DM show that 1-2 months of SGLT-2 inhibitor (including dapagliflozin) therapy results in greater insulin sensitivity and decreased levels of proinflammatory cytokines and free fatty acids (10-15). Recent studies in T2DM human subjects show that 2-4 weeks of SGLT-2 inhibitor therapy improves insulin sensitivity despite an increase in endogenous glucose production (16, 17). However, there are no studies examining the effects of SGLT-2 inhibitor therapy on NFkappaB and other inflammatory mediators in humans with T2DM. Moreover, no studies have examined the effect of SGLT-2 inhibitor therapy on endothelial function in this population. We propose a study to elucidate the anti-inflammatory mechanisms related to SGLT-2 inhibitor therapy in T2DM.

1.2 Research hypothesis

In T2DM subjects on metformin monotherapy, adding dapagliflozin for 12 weeks will reduce monocyte inflammation and improve endothelial function, when compared to adding placebo for 12 weeks.

1.3 Rationale for conducting this study

SGLT-2 Inhibitors reduce hyperglycemia and improve peripheral insulin sensitivity by ameliorating glucotoxicity. Insulin resistance in type 2 diabetes is associated with endothelial dysfunction and vascular inflammation. Thus strategies to improve insulin sensitivity and lower glucotoxicity may improve endothelial inflammation and vascular inflammation. In addition, these SGLT-2 Inhibitors reduce body weight, visceral adiposity, systolic and diastolic blood pressure, microalbuminuria, and oxidative stress. However, the effects of these agents on vascular inflammation and endothelial function is not known in patients with type 2 diabetes although anti-inflammatory properties have been demonstrated in various animal models. In the present study we will assess if dapagliflozin decreases monocyte inflammation and improves endothelial function in patients with type 2 diabetes on metformin

monotherapy. If our hypothesis is confirmed, further studies will be needed to assess the clinical significance of these findings on cardiovascular outcomes in patients with type 2 diabetes and whether SGLT-2 inhibitors can reduce cardiovascular morbidity and mortality.

1.4 Benefit/risk and ethical assessment

Dapagliflozin is associated with:

1. Hypotension: Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating Dapagliflozin, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m2), elderly patients, or patients on loop diuretics.

2. Impairment in Renal Function: Dapagliflozin increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating Dapagliflozin. Before initiating Dapagliflozin, renal function should be monitored and periodically thereafter. Dapagliflozin should be discontinued when eGFR is persistently <60 mL/min/1.73 m2.

3. Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin can increase the risk of hypoglycemia when combined with these agents. The dose of insulin or insulin secretagogue needs to be decreased to reduce the risk of hypoglycemia when used in combination with Dapagliflozin.

4. Dapagliflozin increases the risk of genital mycotic infections especially in those patients with a previous history of genital mycotic infections.

5. Increases in Low-Density Lipoprotein Cholesterol (LDL-C): Increases in LDL-C occur with Dapagliflozin.

6. Bladder cancer: Across 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 0.17% of dapagliflozin-treated patients and 0.03% of placebo/comparator-treated patients. After excluding patients in whom exposure to study drug was <1 year at the time of diagnosis of bladder cancer, there were 4 cases with dapagliflozin and no cases with placebo/comparator. Bladder cancer risk factors and hematuria (a potential indicator of pre-existing tumors) were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to dapagliflozin

There are insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. Dapagliflozin should not be used in patients with active bladder cancer. Furthermore, it needs to be used with caution in patients with a prior history of bladder cancer

In a pool of 12 placebo-controlled studies, the most common adverse reactions (≥5%) associated with Dapagliflozin 5 mg, 10 mg, and placebo respectively were female genital mycotic infections (8.4% vs 6.9% vs 1.5%), nasopharyngitis (6.6% vs 6.3% vs 6.2%), and urinary tract infections (5.7% vs 4.3% vs 3.7%).

7. Diabetic Ketoacidosis: The regulatory authorities, such as the FDA and EMA, have issued communications regarding serious and sometimes life-threatening cases of diabetic ketoacidosis (DKA) in patients treated with the sodium-glucose cotransporter-2 inhibitors canagliflozin, dapagliflozin and empagliflozin.

DKA is typically seen in patients with type 1 diabetes but may rarely happen in patients with type 2 diabetes and occurs as a consequence of absolute or relative insulin deficiency. The FDA communication notes that cases of DKA in patients on SGLT2 inhibitors often were atypical in that the patients' blood sugar levels were only slightly elevated. Potential triggers for development of DKA included recognized risk factors such as major illness and reduced insulin doses, as well as reduced food and fluid intake. In the type 2 diabetes clinical development program phase II / III for dapagliflozin, there was one patient with a reported adverse event of diabetes ketoacidosis (who was on insulin treatment) out of a total of 5936 dapagliflozin treated patients (6247 patient years). No cases of diabetes ketoacidosis were observed in the comparator groups with a total of 3403 patients (3638 patient years).

i) The study team will advise patients to alert them and seek medical attention immediately if they experience symptoms consistent with DKA such as: nausea, vomiting, abdominal pain, confusion, change in breathing pattern and unusual fatigue or sleepiness.

ii) The study team will evaluate any patient experiencing the aforementioned signs or symptoms of DKA, even if glucose levels are not high. The study team will discontinue study drug if acidosis is confirmed and take standard clinical measures to treat DKA when it considers this to be a likely diagnosis.

<u>Use in Specific Populations</u>

-Pregnant Women: There are no adequate and well-controlled studies of Dapagliflozin in pregnant women. Consider appropriate alternative therapies, especially during the second and third trimesters.

•Nursing Mothers: It is not known whether Dapagliflozin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Dapagliflzin, it is advised to discontinue nursing or discontinue Dapagliflozin.

•Geriatric Use: A higher proportion of patients ≥65 years treated with Dapagliflozin had adverse reactions related to volume depletion and renal impairment or failure compared to patients treated with placebo. No Dapagliflozin dose change is recommended based on age.

Yet, Phase III clinical trials showed that dapagliflozin reduced fasting and postprandial plasma glucose and significantly reduced HbA1c and was associated with a significant reduction in weight in patients with type 2 diabetes. Thus the benefits outweigh the risks of therapy.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to examine the effects of 12 weeks of dapagliflozin therapy on monocyte inflammation i.e. NFkB (p65) protein in T2DM subjects.

2.2 Secondary objectives

The secondary objectives are to examine the effects of 12 weeks of dapagliflozin therapy on plasma adipocytokines and endothelial function (as measured by flow mediated dilatation) in T2DM subjects.

2.3 Safety objective

To study the safety of dapagliflozin in type 2 diabetes by monitoring for clinical events.

2.4 Exploratory objectives

None

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart (Table 1)

This is a randomized double blind placebo controlled clinical trial. Prior to beginning the study, interested potential subjects will be prescreened via a telephone interview. If the subject meets criteria via telephone interview, he or she will be invited to participate in an hour-long outpatient screening visit (Visit 1). At Visit 1, subjects will be consented for participation in the study. We will then perform a complete history and physical exam and EKG. We will also draw the following baseline fasting labs: complete metabolic panel (glucose, BUN/Creatinine, liver function tests, electrolytes), lipid panel, hemoglobin A1C, complete blood count, urinanalysis, and urine pregnancy test (if applicable). Results will be reviewed. If the subject meets the inclusion and exclusion criteria, then he or she will be invited to participate in the trial. This is a single-center, randomized, placebo-controlled double-blinded prospective trial with a 1:1 allocation ratio. Patients with type 2 diabetes on metformin monotherapy will be enrolled as per the inclusion criteria. At the start of the study (Visit 2), all subjects will receive the following fasting baseline measurements: (i) plasma free fatty acids (FFA), plasma adiponectin, hsCRP, IL-1b, IL-6, TNF-alpha, 15-epi-lipoxin A4, glucose, and insulin; (ii) monocyte isolation from peripheral (venous) whole blood and quantification of monocyte NFkappaB (P65),TLR2, TLR4, SOCS-3, MYD88, and IkB-alpha, and IkB-beta protein as well as expression levels of CD36, MCP-1, MMP-9,VCAM1, ICAM1 and JNK; and (iii)

ultrasound assessment of flow-mediated dilatation (FMD) of the brachial artery per previously validated methods (18, 19). Each subject will be randomized to one of two arms: (1) addition of placebo pill daily for 12 weeks, or (2) addition of dapagliflozin 5 mg daily for 2 weeks followed by 10 mg po daily for 10 weeks (Visit 3). During the entire 12-week treatment period, subjects will return to clinic every 2-4 weeks (Visit 4-7) following an overnight fast for measurement of glucose, kidney function and electrolytes (BMP), body weight, and blood pressure. A urine pregnancy test (if applicable) will also be performed at each visit. At the end of the treatment period of 12 weeks (Visit 7), all subjects will again receive the following fasting measurements: (i) BMP, plasma free fatty acids (FFA), plasma lipids (including triglycerides), plasma adiponectin, hsCRP, IL-1b, IL-6, TNF-alpha, 15-epi-lipoxin A4, glucose, insulin, and HbA1c; (ii) monocyte isolation from peripheral (venous) whole blood and quantification of monocyte NFkappaB (P65), TLR2, TLR4, SOCS-3, MYD88, and IkB-alpha, and IkB-beta protein as well as expression levels of CD36, MCP-1, MMP-9,VCAM1, ICAM1 and JNK; and (iii) ultrasound assessment of flow-mediated dilatation (FMD) of the brachial artery.

3.2 Rationale for study design, doses and control groups

As the study hypothesis is to test whether dapagliflozin decreases vascular inflammation and improves endothelial function at a dose used in the treatment of type 2 diabetes. Patients with type 2 diabetes on metaformin therapy will receive either dapagliflozin or placebo orally for 12 weeks. Dapagliflozin 5 and 10 mg daily is FDA approved for the treatment of type 2 diabetes in patients on metformin therapy.

4. SUBJECT SELECTION CRITERIA

4.1 Inclusion criteria

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

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

2. Men and women, ages 21 to 70 years.

i) Women of childbearing potential (WOCBP) must be using an acceptable method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized.

ii) Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of investigational product.

iii) Women must not be breastfeeding.

3. Patients with Type 2 Diabetes Mellitus with the following parameters at study entry: hemoglobin A1C ranging from 6.5% to 9.0% and a fasting blood glucose ≤ 200 mg/dL.

4. Patients must be on a stable dose of Metformin therapy for 3 months; the dose of metformin will not change for the duration of the study.

5. Patients are allowed, but not required, to be on statins, ACE-inhibitors, and angiotensin-receptor blockers at doses that have been stable for at least the last 3 months prior to enrollment in the study. Doses will not be changed for the duration of the study.

6. Patients must have a BMI between 27-40 kg/m2

7. Patients must have a stable body weight (±4-5 pounds) for three months prior to enrollment in the study.

8. Patients must have a Creatinine Clearance > 60 mL/min (calculated by Cockcroft-Gault formula).

9. Patients must have the following laboratory values: Hematocrit ≥ 34 vol%; S. creatinine < 1.5 mg/dl in men and 1.4 mg/dl in women and Cr Clearance > 60 ml/min; and AST (SGOT) < 2.5 times ULN, ALT (SGPT) < 2.5 times ULN, alkaline phosphatase< 2.5 times ULN.

4.2 Exclusion criteria

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

1. History of Type 1 diabetes mellitus

2. Women who are pregnant or breastfeeding

3. Patients receiving lipid-lowering medications other than statins within the last 3 months

4. Patient receiving SGLT-2 inhibitors, DPP-IV inhibitors, GLP-1 receptor agonists, thiazolidinediones, insulin, sulfonylureas, alpha-glucosidase inhibitors, corticosteroids, immunosuppressive therapy, thiazide or loop diuretics, or hormone replacement therapy within the last 3 months

5. Patient must stop treatment with NSAIDs and antioxidant vitamin supplements at least one week prior to the start of the study

6. Patients with diabetic gastroparesis

7. Patients with current tobacco use

8. Patients with active malignancy

9. Patients with history of urinary bladder cancer

10. Patients with a history of clinically significant heart disease (NYHA III or IV; more than non-specific ST-T wave changes on the EKG), peripheral vascular disease (history of claudication), or pulmonary disease (dyspnea on exertion of one flight or less; abnormal breath sounds on auscultation) will not be studied

11. Subjects with a history of any serious hypersensitivity reaction to dapagliflozin

12. Prisoners, or subjects who are involuntarily incarcerated

13. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

14. Patients with significant cardiac, hepatic or renal disease (Creatinine Clearance < 60 mL/min calculated by Cockcroft-Gault formula) will be excluded.

5. STUDY CONDUCT

5.1 Restrictions during the study

1. Patients will not be allowed to take nonsteroidal anti-inflammatory drugs (NSAID) and antioxidant vitamin supplements during the study.

5.2 Subject enrollment and randomization and initiation of investigational product

5.2.1 Procedures for randomization

Patients will be randomized to one of the two treatment groups: 1. Dapagliflozin or 2. Placebo. Randomization numbers (patient numbers) will be assigned strictly sequentially as patients become eligible for randomization. Randomization will be computer-generated by the research pharmacy, and the investigators will be blinded to the treatment assignments. The research pharmacy will provide the randomization number and the appropriate bottle numbers.

5.3 Procedures for handling subjects incorrectly enrolled<< or randomized>> <<or initiated on investigational product>>

Enrolled patients who ultimately do not meet the inclusion/ exclusion criteria will not undergo further evaluation and be excluded from the study. A log of these subjects will be kept.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The investigators will be blinded to the treatment assignments. The research pharmacy will provide the randomization number and the appropriate bottle numbers.

5.4.2 Methods for unblinding the study

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in a subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the treating physician.

Before breaking the blind of an individual subject's treatment, the investigator should have determined that the information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational Product	Manufacturer	IMP/ NIMP	Type	Route of administration	Formulation	Comment
Dapagliflozin 5 mg	AstraZeneca	IMP	Active Drug	Oral	Film Coated Tablet	Green, plain, diamond shaped
Matching placebo for Dapagliflozin 2.5mg and 5 mg	AstraZeneca	IMP	Placebo	Oral	Film Coated Tablet	Green, plain, diamond shaped
Dapagliflozin 10 mg	AstraZeneca	IMP	Active Drug	Oral	Film Coated Tablet	Green, plain, diamond shaped
Matching placebo for Dapagliflozin 10 mg	AstraZeneca	IMP	Placebo	Oral	Film Coated Tablet	Green, plain, diamond shaped

AstraZeneca will provide the Sponsor with Dapagliflozin and matching placebo tablets. Dapagliflozin and matching placebo tablets will be supplied in bottles, each containing 35 tablets. The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals.

5.5.2 Doses and treatment regimens

Dapagliflozin 5 mg once daily orally for 2 weeks followed by Dapagliflozin 10 mg once daily orally for 10 weeks/ Placebo PO once daily.

5.5.3 Additional study drug

All patients will continue on metformin treatment at their current dose (dose at the time of screening). The dose of metformin will not be changed during the study.

5.5.4 Labeling

Packaging and labeling will be in accordance with applicable local regulatory requirements to protect the blinded nature of the trial. Labeling will be done by the Sponsor. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labeling will not indicate whether the medication is dapagliflozin or placebo.

Dapagliflozin and matching placebo tablets will be supplied in bottles, each containing 35 tablets by AstraZeneca.

Metformin will be provided as a prescription medication from the local pharmacy and billed to the patient or his insurance company.

The study drugs must be swallowed whole with a liquid and not chewed, divided, dissolved, or crushed.

5.5.5 Storage

All study drugs should be kept in a secure place and under appropriate storage conditions. The Investigational Product label on the bottle specifies the appropriate storage.

5.6 Concomitant and post-study treatment(s)

1. 5. Patient must stop treatment with NSAIDs and antioxidant vitamin supplements at least one week prior to the start of the study.

2. No change in the dose of metformin during the 12 week study period.

5.7 Treatment compliance

Treatment compliance will be monitored by drug accountability as well as the patient's medical record.

5.7.1 Accountability

Subjects will be asked to bring any unused study drug to each study visit.

5.8 Discontinuation of investigational product

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

•Withdrawal of informed consent (subject's decision to withdraw for any reason).

• Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.

• Pregnancy: Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on study pregnancy tests for WOCBP enrolled in the study. The investigator must immediately notify AZ if a study subject becomes pregnant.

• Termination of the study by AZ

• Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

• Inability to comply with the protocol.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in section 6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

5.8.1 Procedures for discontinuation of a subject from investigational product

Treatment with metformin should continue during the treatment period per current guidelines. At the end of the study, patients will continue with metformin therapy and follow up with their primary care physician.

5.9 Withdrawal from study

Subjects are eligible to withdraw from this study at any time, for any reason, without impacting standard clinical care. Data collected up to the date of withdrawal from the study will still be used in the data analysis.

The investigator and/or AstraZeneca may decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Reasons for removal for treatment or the study can include any of the following:

- Subject request
- Safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria (list criteria), pregnancy)
- Decision by sponsor (other than subject request or safety concern)
- Death
- Lost to follow-up

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

All data will be recorded in Case Report Forms (CRF) and stored in a secure area accessible only to the study investigators.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrollment procedures

The following procedures are to be completed after informed consent has been obtained:

- Informed Consent Form signed
- Medical history
- Vital signs (eg, blood pressure, heart rate, respiration rate)
- Review for Adverse Events and Serious Adverse Events (only AEs possibly related to study procedures and SAEs are collected)
- Documentation of concomitant medications
- Physical exam
- Body height
- Body weight
- EKG
- blood will be drawn for plasma free fatty acids (FFA), plasma lipids (including triglycerides), plasma adiponectin, hsCRP, IL-1b, IL-6, TNF-alpha, 15-epi-lipoxin A4, glucose, insulin, and HbA1c; monocyte isolation from peripheral (venous) whole blood and quantification of monocyte NFkappaB (P65),TLR2, TLR4, SOCS-3, MYD88, and IkB-alpha, and IkB-beta protein as well as expression levels of CD36, MCP-1, MMP-9,VCAM1, ICAM1 and JNK
- ultrasound assessment of flow-mediated dilatation (FMD) of the brachial artery
- Randomization of treatment assignment
- Investigational product
- Local laboratory Assessments:
  Complete metabolic panel and CBC, HbA1C, Lipids
  Urine pregnancy test (females of childbearing potential only)

6.2.2 Follow-up procedures

- Vital signs (e.g., blood pressure, heart rate, respiration rate)
- Review for Adverse Events and Serious Adverse Events (only AEs possibly related to study procedures and SAEs are collected)
- Blood will be drawn for fasting plasma glucose and kidney function tests (BMP) at each follow up visit (2-4 weeks interval). Urine pregnancy test (women of childbearing potential) will be performed at each follow up visit.

- At the end of the study visit, blood will be drawn for plasma free fatty acids (FFA), plasma lipids (including triglycerides), plasma adiponectin, hsCRP, IL-1b, IL-6, TNF-alpha, 15-epi-lipoxin A4, glucose, insulin, and HbA1c; monocyte isolation from peripheral (venous) whole blood and quantification of monocyte NFkappaB (P65),TLR2, TLR4, SOCS-3, MYD88, and IkB-alpha, and IkB-beta protein as well as expression levels of CD36, MCP-1, MMP-9,VCAM1, ICAM1 and JNK.
- Documentation of concomitant medications and investigational product compliance at each follow up visit.
- ultrasound assessment of flow-mediated dilatation (FMD) of the brachial artery at the end of the study visit.

6.3 Efficacy

Blood samples will be withdrawn from a peripheral vein by a qualified personnel.

Ultrasound assessment of flow-mediated dilatation (FMD) of the brachial artery will be performed by the PI or a trained co-investigator.

6.3.1 Efficacy variable

- Ultrasound assessment of flow-mediated dilatation (FMD) of the brachial artery

-Plasma free fatty acids (FFA), plasma lipids (including triglycerides), plasma adiponectin, hsCRP, IL-1b, IL-6, TNF-alpha, 15-epi-lipoxin A4, glucose, insulin, and HbA1c; monocyte isolation from peripheral (venous) whole blood and quantification of monocyte NFkappaB (P65),TLR2, TLR4, SOCS-3, MYD88, and IkB-alpha, and IkB-beta protein as well as expression levels of CD36, MCP-1, MMP-9,VCAM1, ICAM1 and JNK.

6.4 Safety

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

6.4.1 Definition of adverse events

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

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

6.4.2 Definitions of serious adverse event

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

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

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be evaluated on a continuous basis while the patient is on study and until 30 days after the last dose of study drug.

Follow-up of unresolved adverse events

Patients should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the principal investigator.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- 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 hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drug
- Description of AE.

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

Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE..

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

Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of chest pain should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.4.4 Reporting of serious adverse events

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-866-984-7229

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. AstraZeneca wants to receive SAE that not require expedited reporting quarterly as line listings.

In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements

6.4.5 Laboratory safety assessment

Study drug toxicities will be assessed continuously by the following clinical and laboratory assessments.

For blood volume see Section 7.1.

6.4.6 Physical examination

signs of volume depletion, rash.

6.4.7 Vital signs

respiratory rate >18/ min

6.4.7.1 Pulse and blood pressure

We will report HR >100 bpm, SBP <100 mmHg, DBP <60 mmHg.

6.4.8 Other safety assessments

We will check kidney function (BUN/Creatinine) and electrolytes (sodium/potassium) and fasting plasma glucose (hypoglycemia/hyperglycemia) at screening and at 2-4 weeks interval during the treatment period.

6.5 Patient reported outcomes (PRO)

Not applicable

6.5.1.1 <<Name of PRO method or questionnaire>>

Not applicable

6.6 Pharmacokinetics

None.

6.6.1 Collection of samples

None.

6.6.2 Determination of drug concentration

None.

6.7 Pharmacodynamics

None.

6.7.1 Collection of pharmacodynamic markers

None.

6.8 Pharmacogenetics

None.

6.8.1 Collection of pharmacogenetic samples

None.

6.9 Health economics

None.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

A total of 115 ml of blood will be drawn during the entire study

15 ml of blood will be drawn during the screening visit (Visit 1).

30 ml of blood will be drawn at Visit 2.

10 ml of blood will be drawn and Visit 4 and 5 and 6

40 ml of blood will be drawn at Visit 7.

7.2 Handling, storage and destruction of biological samples

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

None.

7.2.2 Pharmacogenetic samples

None.

7.3 Labeling and shipment of biohazard samples

Local laboratories will be used for analysis of all specimens collected at each participating affiliate site. Each sample will be labeled and coded to protect subject confidentiality.

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7.4 Chain of custody of biological samples

Not applicable

7.5 Withdrawal of informed consent for donated biological samples

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. If the subject withdraws consent for donated samples, and it has not been processed, the request will be honored. If the subject withdraws consent for donated biological samples and it has already been processed, the data collected up to the date of withdrawal will be included in the analysis of the study. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

All potential serious breaches must be reported to AstraZeneca immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure; debarment).

8.2 Ethics and regulatory review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator will also obtain approval of the FDA prior to the start of the study. The trial will be listed on clinicaltrials.gov. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

8.3 Informed consent

Investigators must ensure that subjects (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) before clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.

6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The consent form must also include a statement that AZ and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

8.4 Changes to the protocol and informed consent form

All protocol amendments and revisions to the informed consent must be submitted to the AZ protocol manager and to the IRB/IEC. No protocol amendments will be implemented until written approval has been given by the IRB/IEC, except when necessary to eliminate an immediate hazard to study subjects.

8.5 Audits and inspections

The Investigator will assure that local study staff cooperate with monitoring and audits. The Investigator agrees to allow auditing of all essential clinical study documents by AstraZeneca or its authorized representatives and inspection by the FDA or other appropriate regulatory authorities. Auditing visits by AstraZeneca will be scheduled with the appropriate staff at mutually agreeable times as applicable.

9.0 STUDY MANAGEMENT

9.1 Training of study site personnel

The Investigator will assure research activities, including those study-related duties delegated and will be performed by appropriately qualified individuals. The Investigator will assure that study staff will demonstrate due diligence in recruiting and screening study patients.

9.2 Monitoring of the study

9.21 Source data

The PI and his team will monitor the study on a daily basis. All treatment emergent AEs will be recorded on source documents (i.e. original documents, data, and records). AEs include those reported spontaneously by the subject and those noted incidentally or as observed by the investigator or study personnel. All clinically significant abnormalities noted upon physical examination, or other diagnostic test results should be reported as an AE, except for baseline measurements that may be considered part of the medical history. In addition, all clinically significant AEs that continue at Study Termination will be followed up by the investigator and evaluated with additional tests if necessary, until the underlying cause is diagnosed or resolution occurs. All AEs will be evaluated for intensity and causal relationship with use of the study medication and/or study procedures by the investigator and reported to the Baylor IRB. All SAEs will be reported to the Baylor IRB and the sponsor within 24 hours. In addition, a safety report will be submitted to Baylor IRB annually. Any new information regarding the study medications will be submitted to Baylor IRB.

9.3 Study timetable and end of study

- Subject participation is anticipated to continue for 13 weeks days (+/- 3 days)
- End of Treatment: will occur at week 13 (+/- 3 days).
- End of Study Primary Completion: defined as all the randomized subjects in of the study have either completed all the scheduled visits or have early terminated from the study
- End of Trial: defined as all enrolled subjects of the study have either completed all the scheduled visits or have early terminated from the study.

10. DATA MANAGEMENT

The investigator is responsible for complying with the requirements for all assessments and data collection (including subject's not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments the investigator or study staff can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

11.EVALUATION AND CALCULATION OF VARIABLES

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11.1 Calculation or derivation of efficacy variable(s)

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11.2 Calculation or derivation of safety variable(s)

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11.2.1 Other significant adverse events (OAE)

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11.3 Calculation or derivation of patient reported outcome variables

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11.4 Calculation or derivation of pharmacokinetic variables

None

11.5 Calculation or derivation of pharmacodynamic variable(s)

None

11.5.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

None

11.5.2 Population analysis of pharmacokinetic/pharmacodynamic variables

None

11.6 Calculation or derivation of pharmacogenetic variables

None

11.7 Calculation or derivation of health economic variables

None

12.STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

Between groups comparisons will be made using two-way analysis of variance (ANOVA.) to analyze changes in NFkappaB following dapagliflozin treatment in comparison to placebo (primary efficacy analysis). Secondary efficacy analysis will include the effect of dapagliflozin (versus placebo) on other markers monocyte inflammation. Pre and post treatment within a group will be analyzed using paired t-tests. Mann Whitney will be used for data which is not normally distributed. All statistical analysis will be performed using SAS (Cary, NC).

12.1.2 Safety analysis set

The safety analysis set will include all consented patients regardless of whether or not primary outcome measures were observed. This data set will include all available data for patients who completed the study as well as those who were lost to follow-up, withdrew from the study, or otherwise did not complete the study.

Adverse Events

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Subject incidences of treatment-emergent adverse events, serious adverse events, treatment-related adverse events and adverse events leading to discontinuation of IP will be tabulated by system organ class and preferred term for each treatment group.

Safety Laboratory Parameters

Laboratory parameters will be summarized for each treatment group using descriptive statistics at each scheduled visit.

Vital Signs

Vital signs will be summarized for each treatment group using descriptive statistics at each scheduled visit.

Concomitant medications of interest will be summarized for each treatment group.

12.2 Methods of statistical analyses

Between groups comparisons will be made using two-way analysis of variance (ANOVA.) to analyze changes in NFkappaB following Dapagliflozin treatment in comparison to placebo (primary efficacy analysis). Secondary efficacy analysis will include the effect of Dapagliflozin (versus placebo) on other markers monocyte inflammation. Pre and post treatment within a group will be analyzed using paired t-tests. Mann Whitney will be used for data which is not normally distributed. All statistical analysis will be performed using SAS (Cary, NC).

12.2.1 Interim analyses

None planned

12.3 Determination of sample size

This trial will be conducted as pilot study, as no prior studies have examined the effects of SGLT-2 inhibitor therapy on NFkB and other inflammatory mediators in humans with T2DM. Moreover, no prior studies have examined the effect of SGLT-2 inhibitor therapy on endothelial function in this population. We anticipate a 20% difference in NFkappaB protein between placebo and active treatment groups and 18 subjects in each study arm will yield significant differences between therapy and placebo in regard to our primary endpoint. Sample size is calculated using SigmaPlot software (San Jose, CA). For the two major outcome variables i.e. monocyte NFkappaB protein, the sample size of ~ 18 patients per treatment group (total of 36 patients) will have >90% power to detect a difference in the means of 20%, assuming a standard deviation of 15%, and with alpha= 0.025. Given that we expect about 10% of the patients enrolled may not complete the 3 month study, we would like to enroll 40 patients so that 36 patients may complete the study.

12.4 Data monitoring committee

The study will be monitored by the PI on a daily basis. A Data Safety Monitoring Plan and annual reports will be submitted to the Baylor College of Medicine IRB. A Data Monitoring Committee will be constituted to monitor the study if directed by the BCM IRB..

13.IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Overdose

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

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

13.2 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca. Women of child-bearing potential must not be pregnant or nursing to participate in this study. However, in the event a woman became pregnant we must ensure patient safety. Each pregnancy in a patient on study treatment must be reported to AstraZeneca within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

13.2.1 Maternal exposure

If a pregnancy occurs in a female subject, while the subject is taking protocol-required therapies, it will be reported to AstraZeneca as specified above. In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies and for an additional 15 weeks after the end of treatment with IP and report the pregnancy to AstraZeneca as specified above.

13.2.2 Paternal exposure

If a pregnancy occurs in a female partner of a male subject, while the subject is taking protocol-required therapies, it will be reported to AstraZeneca as specified above. In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies and for an additional 15 weeks after the end of treatment with IP, report the pregnancy to AstraZeneca as specified above.

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Table 1: Time and Event Schedule for Visit Procedures

Procedure	Visit 1 (Screening)	Visit 2	Visit 3 (randomization)	Visit 4	Visit 5	Visit 6	Visit 7
Study week	**-2**	**-1**	**0**	**2**	**4**	**8**	**12**
Obtain Informed Consent	X						
Confirm Eligibility	X						
Medical History	X						
Review Concomitant Medications	X		X	X	X	X	X
Physical Examination	X			X	X	X	X
Vital Signs	X	X	X	X	X	X	X
CBC and 12-Lead Electrocardiogram	X						
Pregnancy Test (a)	X			X	X	X	X
Urinalysis	X						
Lipids, LFTs,	X						
BMP	X			X	X	X	X
HbA1c	X						X
Insulin/Cytokines/FFA/		X					X
Monocyte isolation studies/ Flow mediated dilatation by Ultrasound		X					X
Randomize			X				
Study Drug	METFORMIN		Start dapa 5 mg or placebo	Dapa10 mg or placebo	X	X	STOP
Medication compliance check				X	X	X	X
Assess for adverse events and Home Blood Glucose Monitoring Log			X	X	X	X	X