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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

Abbreviation or special term	Explanation
T1D	Type 1 diabetes
T2D	Type 2 diabetes
CAN	Cardiovascular autonomic neuropathy
CVD	Cardiovascular disease
DDP-4	Dipeptidyl-peptidase-4
SGLT-2	Sodium-glucose transporter-2
CV	Cardiovascular
FDA	Food and drug administration
HR	Heart rate
BP	Blood pressure
RR	Relative risk
AE	Adverse event
HRV	Heart rate variability
CARTs	Cardiovascular autonomic reflex tests
IRB	Institutional review board
LV	Left ventricle
BNP	B type natriuretic peptide
ADA	American Diabetes Association
ULN	Upper limit of normal
PAD	Peripheral arterial disease
MI	Myocardial infarct
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
CBCP	Complete blood count with platelet
CMP	Complete metabolic panel
HbA1c	Hemoglobin A1c
TSH	Thyroid stimulating hormone
ECHO	Echocardiogram
ESC	Electrochemical skin conductance
ECG	Electrocardiography
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
CRF	Case report form
MEND	Metabolism, Endocrinology and Diabetes Division
LF	Low frequency
HF	High frequency
E/I ratio	Expiration/ inspiration ratio

Abbreviation or special term	Explanation
SDNN	Standard deviation of the normal RR interval
rmsSD	Root mean square of the differences of successive RR intervals
EDV	End diastolic volume
ESV	End systolic volume
CO	Cardiac output
TNFα	Tumor necrotic factor-alpha
IL1β	Interleukin 1 beta
IL6	Interleukin 6
MCP-1	Monocyte chemoattractant protein-1
IL8	Interleukin 8
IL17	Interleukin 17
m-CSF	Macrophage colony-stimulating factor
sVCAM-1	Soluble vascular cell adhesion molecule-1
s-ICAM-1	Soluble intercellular adhesion molecule-1
IL10	Interleukin 10
SAE	Serious adverse event
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
ID	Identification
RCR	Responsible conduct of research
MICHR	Michigan Institutes for clinical and Heath research
RHR	Resting heart rate
FBG	Fasting blood glucose
CGM	Continuous glucose monitoring
MACE	Mean amplitude of glycemic excursions
CV	Coefficient of variation
SD	Standard deviation
LBGI	Low blood glucose index
AUC	Area under the curve

1. INTRODUCTION

1.1 Background

Diabetes mellitus contributes substantially to the global burden of disease, with an estimated 415 million people affected worldwide in 2015, and expected to increase to 642 million by 2040 (http://www.diabetesatlas.org/). The majority of these cases are due to type 2 diabetes (T2D). The burden of T2D is driven by health care costs associated with disease management, its progressive course, the high prevalence and risks of chronic complications including diabetic kidney disease, retinopathy, neuropathy and cardiovascular disease (CVD) (http://www.diabetesatlas.org/), and the overall impact on patients' quality of life [1].

Currently, there are multiple FDA-approved agents to treat hyperglycemia in patients with T2D, that include metformin, sulfonylureas, dipeptidyl-peptidase-4 (DPP-4) inhibitors, glinides, thiazolidinediones, insulin, glucagon like peptide receptor agonists, and most recently the sodium-glucose transporter-2 (SGLT-2) inhibitors. These all have been shown to have various degrees of effectiveness in promoting glucose lowering in T2D [2-6].

The SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) reduce hyperglycemia by selective inhibition of glucose reabsorption in renal proximal tubules via sodium-glucose co-transporter 2, and have been approved by FDA as a monotherapy or in combination with other glucose lowering agents in patients with T2D for improvement of glycemic control with a low risk of hypoglycemia (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204629s000lbl.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204042s002lbl.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf) [3-6],while also promoting reductions in body weight and blood pressure (BP) [7, 8]. Potential mechanisms for BP reduction involve several pathways including a modest diuretic effect and weight reduction [9, 10]. In addition, recently reported human data suggest that the BP reduction with the SGLT-2 inhibitors may also be associated with an improvement in arterial stiffness via reductions in insulin dose and improved arterial compliance, a direct effects on vascular smooth muscle relaxation after induction of a negative sodium balance, and a suppression of markers of inflammation and fibrosis, including nuclear factor κβ and collagen IV expression [11]. One interesting observation is that reduction in systolic and diastolic BP with SGLT-2 inhibitors occurred without a compensatory increase in HR [3, 11, 12] and that most benefit was obtained also in patients with some evidence of heart failure [12].

Tighter glucose control has been shown to effectively prevent chronic complications (nephropathy, retinopathy, neuropathy)[13, 14] and CVD in patients with an early course of T2D on metformin treatment arm [15, 16]. However, in patients with more advanced disease, the effects of tight glucose control on preventing CVD were inconsistent [17-19]. In addition, the effects of the specific agents used to treat hyperglycemia on the chronic complications and especially on CVD events in T2D remain uncertain, with some agents showing some potential benefit [15, 20] while most had been neutral [13, 21-23].

However, most recently beneficial effects on CVD events were reported with a SGLT-2 inhibitor, empagliflozin, in patients with T2D at high risk of CVD events [12]. The Empagliflozin: Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial, a randomized double-blind placebo-controlled trial, reported significant reduction of death from cardiovascular cause (38% RR), all-cause mortality (32% RR) and hospitalization for heart failure (35% RR) in patients with T2D in empagliflozin treatment arms [12].

The exact mechanisms of the beneficial effects on cardiovascular outcomes is not yet understood, although their effects on body weight, glucose control and blood pressure (BP) reduction were suggested [7, 10, 12].

1.2 Research hypothesis

We hypothesize that the potential benefits of SGLT-2 inhibitors on cardiovascular outcomes in patients with T2D are due to modulatory effects on the sympathetic/parasympathetic imbalance, and cardiovascular autonomic neuropathy (CAN) as suggested by a blunting in the expected compensatory increase in HR associated with BP lowering.

1.3 Rationale for conducting this study

As mentioned above reduction in systolic and diastolic BP with SGLT-2 inhibitors occur without a compensatory increase in HR [3, 11, 12]. In addition, in the EMPA-REG trial the CVD outcome was driven by a reduction in CVD related death and most benefit was observed in patients with evidence of heart failure [12]. Although glucose control, reduction in BP and weight loss have all been considered for beneficial effects onCVD, other classes of above agents also reduce glucose, BP, and some body weight, while similar effects on CVD were not reported [23], except for the recent report of Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes [24].

Thus, to test the above hypothesis we plan to evaluate potential mechanisms that could explain the CVD benefits with SGLT-2 inhibitors. We plan to specifically test in this study whether these benefits may be due to changes in the sympathetic/parasympathetic function and thus protect against arrhythmia and /or progression of myocardial dysfunction. We plan to perform a randomized, single-blinded to the investigators, open-label, 2-period crossover phase IV clinical trial comparing 12-weeks of glycemic intervention with a SGLT2 inhibitor, dapagliflozin versus a sulfonylurea, glimepiride on measures of heart rate variability (HRV). The rationale for using an active comparator is to maintain similar levels of glucose control with the interventions and thus account for the effects of reduction in blood glucose on measures of CAN, and the current evidence demonstrates similar glucose lowering effects between SGLT2 inhibitors and sulfonylureas [25]. In addition, sulfonylureas are very commonly used in treating T2D in clinical practice. Given some potential detrimental CVD effects described with glyburide or glipizide [26, 27], we have elected to use glimepiride in this study to evaluate the changes in measures of CAN during these different interventions.

We also plan to evaluate the indices of glucose variability and its association with changes in CAN parameters in patients with type 2 diabetes during each dapagliflozin and glimepiride treatment period. Glucose variability is also associated with an increased risk of hypoglycemia, which is an important barrier in sustaining intensive treatment in patients with diabetes [28, 29]. Recurrent severe hypoglycemia, besides inducing alterations in cardiac electrical stability and QT interval prolongation, may contribute to alter the cardiac autonomic function and the cardiovagal balance, increasing the risk of cardiac arrhythmia in patients with diabetes [30, 31] Theoretically, given the higher propensity for hypoglycemia, sulfonylurea may induce more glycemic variability than SGLT-2 inhibitors. Currently no studies evaluated directly the changes in daily glucose excursions with these commonly prescribed agents were done. Thus, adding a component continuous glucose monitoring with the Abbott's Freestyle Libre Pro for 2 weeks during each sulfonylurea and SGLT-2 inhibitor intervention phase in this T2D cohort, will enable performing additional analyses linking effects of medications on daily glucose profiles with measures of heart rate variability and heart function, that could unveil important data on CVD risk with a minimal additional cost.

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1.4 Benefit/risk and ethical assessment

1.4.1 Risks Associated with Study Participation

Risks associated with study participation in general are related to the time commitment for the study, and risk for loss of privacy. There will be nine "in-person" visits required for the study. The study staff will try to minimize the burden of the visits to the extent practical by scheduling on days and at times that are most convenient for the patient. Privacy risks will be reduced by maintaining a separate research record that uses a coded identifier, rather than personal identities. Links to the coded identifier and personal identity shall be maintained in a secure electronic file by the study coordinator and the links will ultimately be destroyed. Destruction of the links will occur no sooner than 2 years after the study has been acknowledged as terminated by the University of Michigan Institutional Review Board (UM IRB).

1.4.2 Risks Associated with Blood Collection

Risks associated with blood collection are pain, discomfort, bleeding, bruising or infection. There is also the risk of dizziness, light-headedness, nausea or even fainting. Blood sampling will be performed by staff with skill and experience in venipuncture.

1.4.3 Risks Associated with Study Medications

The study medications, dapagliflozin and glimepiride, are very effective in glucose lowering. However, because of glucose lowering agents, they are also associated with hypoglycemia in general. However, because of the mechanism of action of dapagliflozin

(SGLT-2 inhibitor), the risk of hypoglycemic episodes is considered to be low. The recommended starting dose of dapagliflozin is 5 mg daily and glimepiride 1-2 mg daily. Therefore, we will start with low dose and titrate it up to optimal dose (dapagliflozin 10 mg daily and glimepiride 4 mg daily) based on participants' glucose monitoring and control to minimize hypoglycemic episodes. Symptoms attributed to hypoglycemia as well as glucose levels will be closely monitored in the trial.

Other potential risks of **dapagliflozin** are volume depletion, diabetes ketoacidosis, urinary tract and genital infection and hypotension. Subjects will be advised to maintain adequate fluid intake and monitor BP closely during study periods. If the study participant develops any of the mentioned risks, he/she will be managed and monitored according to standard care.

The common potential side effects of FDA approved **glimepiride** are hypersensitivity reaction and gastrointestinal reactions. All participants will be notified of risks of the study medications and are required to report to us as soon as they notice. The study personnel will report all directly observed adverse events and all adverse events spontaneously reported by the trial subject to University of Michigan IRB as adverse events (AE) and record those in CRF. All patients participating in this study will be treated in accordance to best standard of care per American Diabetes Association guidelines and recommendations.

All the participants will receive both study medications equally (12-week intervention period) in certain order. Both the study medications are proved to be effective in lowering glucose. In addition, the patients taking part in the trial may derive general medical benefit from careful and close monitoring by medical personnel during the study. Safety will be ensured by monitoring the subjects for AEs both clinically and by laboratory testing and by the home blood glucose monitoring. Participation in the study is completely voluntary and the participant can withdraw anytime from the study if one does not want to continue study medications either due to adverse events or other reasons. The study will potentially benefit to the diabetes society as it will reveal the important information regarding the potential mechanism of dapagliflozin (SGLT-2 inhibitor) on sympathetic/parasympathetic tone, and this may further contribute to the potential benefits on cardiovascular outcomes in patients with diabetes.

1.4.4 Risk Associated with Cardiovascular Autonomic Testing

Participants will be asked to fast in preparation for testing and are therefore at risk for hypoglycemia. Testing will be scheduled in the morning to shorten the duration of fasting. The test itself has few risks associated with it, although some patients may become dizzy or lightheaded when moving from supine to standing, or after performing Valsalva maneuvers. Subjects will be reminded to report any dizziness or lightheadedness immediately to the examiner and will be instructed to return to a seated or lying position as needed to relieve symptoms.

1.4.5 Risk Associated with Wearing Continuous Glucose Monitoring Device

Participants will be provided with a Freestyle Libre Pro CGM for monitoring of interstitial glucose every 5-minute interval for 14 days during each study intervention phase. There is a very low risk for developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies.

During follow-up visit, the site where a CGM sensor has been worn will be carefully assessed by study personnel.

2. STUDY OBJECTIVES

The main objective of this study is to evaluate the effects of dapagliflozin vs active comparator, glimepiride on measures of CAN, and indirectly on CVD outcomes in patients with T2D.

2.1 Primary objective

Evaluate the effects of 12-week treatment with dapagliflozin 5 mg daily escalating to 10 mg daily on measures of CAN as assessed by changes in HRV, changes in cardiovascular autonomic reflex tests (CARTs) and resting heart rate (RHR) compared with 12-week treatment with glimepiride 2 mg daily escalating the dose to 4 mg (no more than 4 mg daily) as needed based on glucose monitoring and control.

2.2 Secondary objectives:

Evaluate the effects of 12-week glycemic interventions on glucose control, BP, and weight.

2.3 Safety objective:

Evaluate the following parameters:

1. Incidence of symptomatic and asymptomatic hypoglycemia, glucose ≤ 70 mg/dl, as defined by American Diabetes Association (ADA)

2. Incidence of sever hypoglycemia as defined by hypoglycemia requiring assistance from another person. It is also characterized by cognitive impairment that may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death, and it is reversed by administration of glucose.

3. UTIs

4. Any other AEs (see Section 1.4)

2.4 Exploratory objectives

We will evaluate the effects of dapagliflozin on measures of cardiac function. We will assess the B type natriuretic peptide (BNP), a sensitive biomarker for left ventricle function and prognosis and risk stratification [32, 33] at baselines and 12 weeks after each study drug (2 periods).

We will use a 14-day continuous glucose monitoring (CGM) using Abbott's Freestyle Libre Pro to evaluate and compare the indices of glucose variability [mean glucose, standard deviation (SD), coefficient of variation (CV), the mean amplitude of glycemic excursions (MAGE), low blood glucose index (LBGI) and area under the curve (AUC) for hypoglycemia] during each dapagliflozin and glimepiride intervention phase in patients with type 2 diabetes and also assess the association between the indices of glucose variability and changes in measures of HRV during each intervention period.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This is a 26-week, single-center, randomized, single-blinded to the investigators, open-label, 2-period crossover phase IV clinical trial comparing 12-weeks of glycemic intervention with dapagliflozin versus glimepiride on measures of HRV. The two periods will be separated by a 2-week wash-out period. All subjects will be allocated and randomized to each treatment sequence in a 1:1 fashion. Participants will receive either dapagliflozin 5 mg or glimepiride 2 mg daily initially for 4 weeks then titrating the dose gradually up to dapagliflozin 10 mg daily or glimepiride 4 mg daily (no more than 4 mg daily) as needed based on glucose monitoring for 8 more weeks (total 12 weeks) followed by 2-week washout period. Then they will receive the study drugs in reverse order to the first period for another 12 weeks. Glucose variability will be also assessed using Abbott's Freestyle Libre Pro CGM for 2-week during each intervention period.

Figure 1: Proposed study design

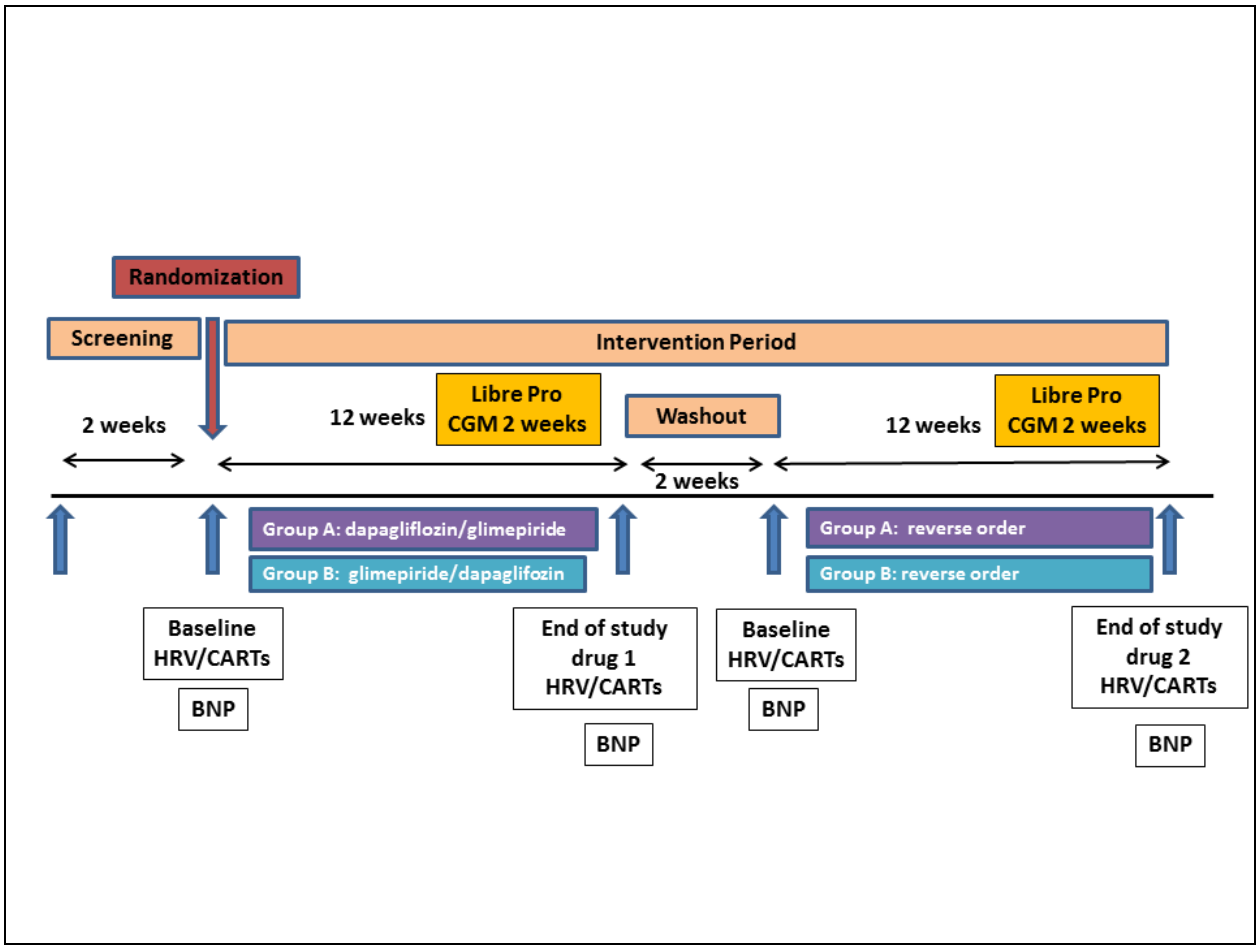

Table 1: Proposed visit schedule

		Period 1				Wash -out	Period 2			
Visit Numbers	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		Visit 6	Visit 7	Visit 8	Visit 9
Visit Description	Screening	Baseline Visit (Study Drug 1)	Monitoring	Monitoring	End of Study Drug 1	N/A	Baseline Visit (Study Drug 2)	Monitoring	Monitoring	End of Study Drug 2
Time point	Day -30 to 0	Day 0	Week 4	Week 8	Week 12	Week 13-14	Week 15	Week 19	Week 23	Week 26
Visit window	1 month	± 7 days	± 7 days	± 7 days	± 7 days	NA	± 7 days	± 7 days	± 7 days	± 7 days
Informed consent and HIPPA[1]	X									
Medical history	X				X		X			X
Physical exam[2]	X				X					X
Inclusion/Exclusion criteria	X									
Concomitant medications	X						X			
Vital signs	X	X	X	X	X		X	X	X	X
Urine analysis, urine β-HCG test in women of childbearing age	X									
Venous blood A1C	X				X					X
CBCP, FBG, comprehensive metabolic profile, , lipid profile, and urine albumin excretion	X				X					X
TSH	X									
BNP	X				X		X			X

ECG	X				X		X			X
HRV		X			X		X			X
CARTs		X			X		X			X
CGM				2 weeks					2 weeks	
Assess hypoglycemia		X	X	X	X		X	X	X	X
Record Adverse Events (AEs), Serious Adverse Events (SAEs)		X	X	X	X			X	X	X
Assessment of compliance by counting pills			X	X	X			X	X	X

[1] The informed consent form must be signed before any study procedure is performed.

[2] Physical exams will include vital signs, height and weight measurements, as well as comprehensive systematic examination.

3.2 Rationale for study design, doses and control groups

See above (section 1.3) regarding overall study design and comparator group.

The dose titration algorithm described above was selected to target equal glycemic lowering effects for avoiding confounding effects and for ethical considerations. To prevent hypoglycemic episodes, we will initiate a lower dose for both study medications (dapagliflozin 5 mg and glimepiride 2 mg), and will escalate the dose gradually up to 10 mg dapagliflozin and glimepiride 4 mg daily (no more than 4 mg daily) as needed based on daily glucose monitoring and profile of AEs (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf).

4. SUBJECT SELECTION CRITERIA

We plan to enroll 45 subjects with type 2 diabetes mellitus (T2D) in this study (see below power calculation) with the following eligibility criteria.

4.1 Inclusion criteria

1. Patients with type 2 diabetes as defined [34] on background metformin monotherapy who are not meeting ADA standard of care recommended glucose target [34]

2. Age ≥18 years

4.2 Exclusion criteria

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

1. History of recurrent urinary tract infections
2. Patients with mycotic infections especially genital infection.
3. Severely hypotensive patients
4. History of unexplained microscopic or gross hematuria, or microscopic hematuria at visit 1, confirmed by a follow-up sample
5. Presence of hypersensitivity to dapagliflozin or other SGLT2 inhibitors (e.g. anaphylaxis, angioedema, exfoliative skin conditions)
6. Inability or refusal to comply with protocol
7. Current participation or participation in an experimental drug study in previous three months
8. Presence of history of diabetic ketoacidosis
9. Planned cardiac surgery or angioplasty within 3 months
10. Recent history of acute CV events such as MI, stroke, PAD within 3 months prior to enrollment
11. Patients with severe renal impairment or unstable or rapidly progressing renal disease or end stage renal disease.
12. Clinical conditions that could interfere with the cardiovascular autonomic function and heart rate variability (arrhythmias)
13. Severe hepatic insufficiency and/or significant abnormal liver function (defined as aspartate aminotransferase >3× upper limit of normal (ULN) and/or alanine aminotransferase >3× ULN) or creatinine kinase >3× ULN.
14. History of cancer other than basal cell carcinoma and or treatment for cancer within the last 5 years
15. Women of child-bearing potential who may be pregnant or lactating.
16. History of pancreas, kidney or liver transplant.

17. History of drug or alcohol abuse within 5 years

18. History of allergy to sulfa drugs

19. Presence of any condition that, in the opinion of the investigator would make it unlikely for the subject to complete the study.

20. Congestive heart failure (CHF) defined as New York Heart Association class III and IV

5. STUDY CONDUCT

5.1 Restrictions during the study

All consented study patients are required to comply with the study protocol. Participation in other interventional research studies is completely restricted to participants. Glycemic intervention with additional antidiabetic medications other than metformin is prohibited. See above exclusion criteria in section 4.2.

Medications that can interfere with the study procedures such as beta blockers, weight loss medications etc. are restricted during the study due to their influence on procedures for cardiovascular autonomic function. Systemic steroids are also prohibited due to the influence on glucose metabolism.

Participants are also required to fast overnight the day before CAN testing and blood draw. Women of child-bearing potential must continue to practice an acceptable method of birth control throughout the study periods.

5.2 Subject enrollment and randomization and initiation of investigational product

5.2.1 Procedures for randomization

Subjects will be proceeded to visit 2-baseline visit (study drug 1) after they pass the screening visit (visit 1).

Randomization to dapagliflozin or glimepiride: After signing informed consent, confirming eligibility and completion of baseline assessments (visit 2), subjects will be randomized in a 1:1 fashion to either open-label dapagliflozin 5 mg daily or open-label glimepiride 2 mg daily for 4 weeks and escalate the dose gradually up to dapagliflozin 10 mg daily or glimepiride 4 mg daily (no more than 4 mg daily) as needed based on their glucose monitoring. Patients will be asked to check glucose in the morning and before dinner. Fasting glucose should be between 80-130 mg/dl and daytime glucose should be in the range of 80-160 mg/dl.

Procedure for Subject Treatment Assignment: Subjects will be randomized to treatment with either dapagliflozin or glimepiride. The procedures for randomization will be determined by the study biostatistician. The study drugs will be dispensed by the research pharmacy.

5.2.2 Study Visits

The schedule of study visits is shown in Table 1. After obtaining informed consent, verifying eligibility at screening and completing all required baseline assessments, subjects will be randomized and provided with study medications. Patients will be also followed every 4 weeks in each study drug period. The staff should query the subject regarding any changes to their health, changes to their medication regimen, and frequency and severity of hypoglycemia at each visit.

Visit 1: Screening/Eligibility (Day -30 to 0)

An eligibility visit will be scheduled for subjects who, based on preliminary screening (telephone, email, medical chart review), meet the general entry criteria (refer to inclusion criteria). At Visit 1 the investigator or her designee will obtain written informed consent, after which all required eligibility examinations will be performed. The eligibility examination will include the following laboratory assessments: Hemoglobin A1c (HbA1c), comprehensive metabolic panel (CMP) including FBG, complete blood count with platelets (CBCP), thyroid stimulating hormone (TSH), lipid profile, B type natriuretic peptide (BNP), urine albumin assessment, urine analysis and in all women of child bearing age and potential, a urine pregnancy test, even if an accepted method of contraception is being used. If any of the required laboratory measures are documented in the subject's medical record as being completed in the prior 3 months (1 month for HbA1c, and 6 months for urine albumin), they will not need to be repeated at the screening visit.

Weight, height and seated blood pressure and pulse will be obtained. A structured history and physical examination and electrocardiogram will be performed at the screening visit. All visit 1 measures are to be completed at one visit.

Visit 2- Baseline Visit (Study Drug 1) (Day 0)

This study will include CAN assessments (see section 5.2.3), meter download for evaluation of hypoglycemia at baseline and to initiate treatment with either dapagliflozin or glimepiride.

Upon satisfactory completion of all eligibility and baseline visit (study drug 1) assessment, a 12-week supply of dapagliflozin 5 mg tablet or glimepiride 2 mg tablet will be provided, and written instructions for use of the medication reviewed with and provided to the subject. Subjects will be instructed to take dapagliflozin 5 mg daily or glimepiride 2 mg daily with or without food in the morning once daily for 4 weeks then escalating the dose up to dapagliflozin 10 mg daily or glimepiride 4 mg (no more than 4 mg daily) as needed based on glucose monitoring and control. Participants will be instructed to monitor glucose 2 times

daily, fasting glucose and before dinner with the goal of fasting glucose between 80-130 mg/dl and of pre-meal glucose between 80-180 mg/dl. Participants will be asked to record glucose data and the number of doses taken every day on a log that will be provided. Participants will be also asked to bring a glucometer with them for each visit. Subjects are to be reminded to return any unused study medication at their next visit. Adverse events will be recorded and reported as required.

Study staff will contact the subject within one week of the Visit 2 to assess medication compliance and tolerance.

All subjects in group A and B will be allocated and randomized to each treatment sequence in a 1:1 fashion. Participants will receive either dapagliflozin 5 mg or glimepiride 2 mg daily initially for 4 weeks then titrating the dose based on blood glucose levels up to dapagliflozin 10 mg daily or glimepiride 4 mg (no more than 4 mg daily) for 8 more weeks (total 12 weeks) followed by a 2-week washout period. Participants will then receive the study drugs in reverse order to the first study drug period during second crossover period for another 12 weeks.

Visit 3: Safety Monitoring (Study Drug 1) (Week 4)

At this visit, the study staff will obtain vital signs (weight, blood pressure, resting heart rate) and will ask the subject about any changes in health status or physical symptoms and record the findings in the source documents. Glucometers will be downloaded and incidence of hypoglycemia will be evaluated. The staff will assess compliance with study drug and tolerance. Adverse events will be recorded and reported as required.

Visit 4: Safety Monitoring (Study Drug 1) (Week 8)

At this visit, the study staff will obtain vital signs (weight, blood pressure, resting heart rate) and will ask the subject about any changes in health status or physical symptoms and record the findings in the source documents. Glucometers will be downloaded and incidence of hypoglycemia will be evaluated. The staff will assess compliance with study drug and tolerance. Adverse events will be recorded and reported as required. Urine pregnancy testing may be performed at the discretion of the investigator for all women of childbearing potential.

Participants will be provided with a Freestyle Libre Pro CGM to collect glucose data for 2 weeks following this visit. Libre Pro CGM will be placed on the participants by trained study personnel during this visit. Freestyle Libre Pro CGM is very simple to use and does not require glucose calibration or participant's operation. Then participants will also be asked either to mail the CGM or to bring the CGM with them in next visit.

Visit 5: End of Study Drug 1 (Week 12)

At this visit, the following will be performed: vital signs (weight, blood pressure, resting heart rate), a structured history and physical examination, electrocardiogram, information about any adverse events, all CAN assessments (see section 5.2.3), meter

download for evaluation of hypoglycemia, blood draw for HbA1c, BNP, and safety laboratory assessments (CMP including FBG, CBCP, urine albumin assessment and lipid profile). The study staff will collect any unused study medication. The number of unused dapagliflozin or glimepiride tablets will be recorded in the source document and unused medication secured until returned for final drug disposition. During this visit, the site where a CGM sensor has been worn will be carefully assessed by study personnel.

Wash-out period

A 2-week wash-out period will be followed after first study drug period.

Visit 6: Baseline Visit (Study Drug 2) (Week 15)

At this visit, the following will be performed: vital signs (weight, blood pressure, resting heart rate), a structured history, information about any adverse events, electrocardiogram, all CAN assessments (see section 5.2.3), meter download for evaluation of hypoglycemia and blood draw for BNP. The key activity of this visit is to re-initiate treatment with either dapagliflozin or glimepiride. After a 2-week wash-out period, visit 6-baseline visit (study drug 2) will be initiated. Participants will again receive study drugs (dapagliflozin or glimepiride) in a reverse order to the first study drug period for another 12 weeks. Urine pregnancy testing may be performed at the discretion of the investigator for all women of childbearing potential.

A 12-week supply of dapagliflozin 5 mg tablet or glimepiride 2 mg tablet will be provided, and written instructions for use of the medication reviewed with and provided to the subject. Subjects will be instructed to take dapagliflozin 5 mg or glimepiride 2 mg with or without food in the morning daily for 4 weeks then escalating to dapagliflozin 10 mg daily or glimepiride 4 mg (no more than 4 mg daily) as needed based on glucose monitoring and control. Participants will be asked to record the number of doses taken every day on a log that will be provided. Subjects are to be reminded to return any unused study medication at their next visit.

Study staff will contact the subject within one week of the Visit 6 to assess medication compliance and tolerance.

Visit 7: Safety Monitoring (Study Drug 2) (Week 19)

At this visit, the study staff will obtain vital signs (weight, blood pressure, resting heart rate) and will ask the subject about any changes in health status or physical symptoms and record the findings in the source documents. Glucometers will be downloaded and incidence of hypoglycemia will be evaluated. The staff will assess compliance with study drug and tolerance. Adverse events will be recorded and reported as required.

Visit 8: Safety Monitoring (Study Drug 2) (Week 23)

At this visit, the study staff will obtain vital signs (weight, blood pressure, resting heart rate) and will ask the subject about any changes in health status or physical symptoms and record the findings in the source documents. Glucometers will be downloaded and incidence of hypoglycemia will be evaluated. The staff will assess compliance with study drug and tolerance. Adverse events will be recorded and reported as required. Urine pregnancy testing may be performed at the discretion of the investigator for all women of childbearing potential.

Participants will be provided with a Freestyle Libre Pro CGM to collect glucose data for 2 weeks following this visit. A Libre Pro CGM will be placed on the participants by trained study personnel during this visit. Freestyle Libre Pro CGM is very simple to use and does not require glucose calibration or participant's operation. Then participants will also be asked either to mail the CGM or to bring the CGM with them in next visit.

Visit 9: End of Study Drug 2 (Week 26) or Final Visit

At this visit, the following will be performed: vital signs (weight, blood pressure, resting heart rate), a structured history and physical examination, information about any adverse events, electrocardiogram, all CAN assessments (see section 5.2.3), meter download for evaluation of hypoglycemia, blood draw for HbA1c, BNP, and safety laboratory assessments (CMP including FBG, CBCP, urine albumin assessment and lipid profile). The study staff will collect any unused study medication. The number of unused dapagliflozin or glimepiride tablets will be recorded in the source document and unused medication secured until returned for final drug disposition.

The study staff will collect any unused study medication. The number of unused dapagliflozin or glimepiride tablets will be recorded in the source document and unused medication secured until returned for final drug disposition. The subjects will be again assessed for adverse events.

During this visit, the site where a CGM sensor has been worn will be carefully assessed by study personnel.

Within 1 week of the final visit, the study staff will contact the subject by phone or email to inquire about any changes in health status.

5.2.3 Assessments

CAN

A. Heart rate variability (HRV) studies: low and high frequency power (LF,HF), and time domain measures of HRV, standard deviation of normal RR interval(SDNN), root mean square of successive RR intervals (RMSSD) are analyzed from continuous ECG recordings using the ANX 3.1 software (ANSAR Inc., Philadelphia , PA) as described [35, 36].

B. Cardiovascular reflex tests will include: 1) changes in R-R interval with deep breathing, a measure of sinus arrhythmia during quiet respiration reflecting primarily parasympathetic function; 2) the R-R response to standing, inducing reflex tachycardia followed by

bradycardia which is jointly vagal and baroreflex-mediated; 3) the Valsalva ratio which evaluates cardiovagal function in response to a standardized increase in intrathoracic pressure (Valsalva Maneuver); and 4) orthostatic changes in BP. These tests are reproducible and considered as gold-standard [36, 37].

C. Resting heart rate

Subjects will be asked to avoid food, caffeine and tobacco products for at least 8 hours prior to testing, and hold any medication until testing was completed. Subjects who experienced a hypoglycemic episode after midnight [blood glucose ≤ 50mg/dl (2.77mmol/l)] prior to the testing were rescheduled.

Cardiac function

We will measure serum BNP, by Chemiluminescent Immunoassay (CLIA) (Siemens, Erlangen, Germany) and will evaluate changes in BNP, as a biomarker for LV function. The blood draw will be performed at baseline and end of each study drug period.

Assessment of glucose variability

We will use a 14-day continuous glucose monitoring (CGM) using Abbott's Freestyle Libre Pro to evaluate and compare the indices of glucose variability [mean glucose, standard deviation (SD), coefficient of variation (CV), the mean amplitude of glycemic excursions (MAGE), low blood glucose index (LBGI) and area under the curve (AUC) for hypoglycemia] during each dapagliflozin and glimepiride intervention phase in patients with type 2 diabetes and also assess the association between the indices of glucose variability and changes in measures of HRV during each intervention period.

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

The data management plan for this project is based on the randomization of 45 participants, with randomization occurring at the time of Visit 2. All candidates who complete the informed consent process will be assigned a study identification number (ID) at the time of Visit 1. Unless otherwise stipulated by the sponsor-investigator, the ID numbers are patient-specific and will be retained and associated with candidates who fail screening or are found to be ineligible, and/or drop-out prior to randomization. Follow-up will not be continued for candidates who do not proceed to randomization. Follow-up and research activities will be pursued on all randomized participants, even those candidates who may for some reason stop research medications.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The investigators will be blinded to the study drugs. The research pharmacy and participants will know the study drugs that participants will be on. The research pharmacy will be dispensing the study medications per the randomization schedule that will be provided by the study biostatistician.

5.4.2 Methods for unblinding the study

In the event of an emergency and a need to know study medications, the investigator will contact the Research Pharmacist and request identification of subject's test article assignment. The Research Pharmacist will indicate that the blind was broken on the Pharmacy Randomization Log and will document the date of the request, the name of the research personnel making the request, and the pharmacist's signature. The research coordinator will report the emergent event on the Adverse Event CRF and the unmasking event on the Unmasking Report CRF and then signed by the investigator.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Dapagliflozin 5 mg tablet

Dapagliflozin is a sodium glucose trasporter-2 (SGLT-2) inhibitor, a new class of glucose lowering agent that reduces hyperglycemia in patients with T2D by reducing renal glucose reabsorption.

Investigational product	Dosage form and strength	Manufacturer
Dapagliflozin	5 mg tablet	AstraZeneca
Glimepiride	1 mg tablet	Sanofi Aventis

5.5.2 Doses and treatment regimens

Participants will receive either open-label dapagliflozin 5 mg or open-label glimepiride 2 mg daily initially for 4 weeks then titrating the dose based on blood glucose levels up to dapagliflozin 10 mg daily or glimepiride 4 mg (no more than 4 mg daily) daily for 8 more weeks (total 12 weeks) followed by a 2-week washout period and then participants will receive the study drugs in reverse order to the first period for another 12 weeks.

5.5.3 Additional study drug

Glimepiride 2 mg tablet

Glimepiride is a sulfonylurea agent that reduces hyperglycemia in patients with T2D by stimulating insulin release from the pancreatic beta cells and reduction of glucose output from the liver.

5.5.4 Labeling

The label will include the following information: trial number, medication number.

Each medication box will contain an appropriate amount of dapagliflozin or glimepiride tablets, plus some reserve, for dosing until the next scheduled visit. Study drug will be supplied on a per Visit basis. Supply will be managed by University of Michigan Health System (UMHS) research pharmacy.

5.5.5 Storage

Dapagliflozin film-coated tablets and glimepiride tablets should be stored at 15° to 25°C (59° to 77°F) in a tightly closed container. The minimum/ maximum storage temperature must be measured and documented at least weekly by investigational drug store manager or pharmacist. All study medications will be contained in medication boxes identified with the trial number and medication number.

5.6 Concomitant and post-study treatment(s)

The research staff will record all concomitant drugs used by the subject in the source documents. This is to include prescription, non-prescription, homeopathic medications and dietary/vitamin supplements. At the screening visit, medication use is to be carefully reviewed to ensure that no contraindicated medications as described in the protocol are being used (e.g., beta blocker agents, phentermine). At all subsequent visits, subjects will be asked to report any changes to their reported medication use and the source document updated accordingly. Queries regarding medication exclusions and contraindications are directed to the study principle investigator.

5.7 Treatment compliance

Study staff will contact the subject within one week of initiating study medications to assess medication compliance and tolerance. All patients will be asked to bring their study medications with them to each study visit. The study staff will assess medication compliance and tolerance at each visit. Patients will be reminded about purpose of the study and importance of compliance with the study medications at each visit. Adverse events will be similarly recorded and reported as required. The study staff will also collect any unused study medication at the end of each intervention period. The number of unused dapagliflozin or glimepiride tablets will be recorded in the source document and unused medication secured until returned for final drug disposition.

5.7.1 Accountability

The pharmacist / investigational drug storage manager must maintain records of the trial medication's delivery to the trial site, the inventory at the site, the use by each patient, and destruction of unused medication. Proof of destruction will be provided to AstraZeneca at the end of the study. These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product and trial patients. The pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the study protocol and reconcile all investigational products.

5.8 Discontinuation of investigational product

The study drugs will be discontinued in the following conditions:

1. Study patient withdraws consent.
2. Study patient fails to comply with the study protocol.
3. Study subject becomes pregnant.
4. If the study patient will need to be on concomitant drugs that may interfere with the study findings or study medications that may lead to higher risk of hypoglycemia, the study medication can be discontinued.
5. If the study patient develops persistent or recurrent serious side effects as described above (Section 1.4, 6.4.2 and 6.4.4), study drugs will be discontinued permanently.

5.8.1 Procedures for discontinuation of a subject from investigational product

If the study patient withdraws consent or who fails to comply with the study protocol or becomes pregnant, participation in the study will end and the study medication will be stopped. No further evaluation will be performed and no attempts should be made to collect additional data.

If a patient develops UTI or genital infection, we will manage the infection according to standard of care. However, a patient with persistent or recurrent UTI or genital infection despite standard of care, study medications will be hold temporarily until infections resolve. If a patient develops persistent serious adverse effects from study drugs (section 6.4.2 and 6.4.4), study medications will be discontinued permanently. And patients will be followed up until their serious adverse effects are completely resolved.

5.9 Withdrawal from study

A subject may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or

administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible.

If the subject withdraws consent, no further evaluations should be performed and no attempts should be made to collect additional data; however, they may be questioned regarding their reason for withdrawal and asked to return all unused investigational products.

Patients who withdraw or discontinue from the trial after randomization will not be replaced.

6. COLLECTION OF STUDY VARIABLES

We will collect the following variables for primary and secondary endpoints:

Primary Endpoints:

Changes in measures of HRV as defined by: Frequency domain measures of HRV (continuous variables): high frequency (HF) power (0.04-0.15 Hz) (ms2); low frequency (LF) power (0.15-0.4 Hz) (ms2) as measured by the LF:HF ratio. The primary outcome will be the difference of the LF:HF ratio from baseline to 12 weeks between the two drugs (periods).

Secondary Endpoints:

1) Changes in measures of HRV as defined by: Time domain measures of HRV (continuous variables): (i) standard deviation of the normal RR interval (SDNN) (msec) and (ii) root mean square of the differences of successive RR intervals (rmsSD) (msec)

2) Changes in CARTs as defined by: i) expiration/inspiration (E/I) ratio, ii) Valsalva ratio and iii) 30:15 ratio

3) Changes in BNP with each intervention as a measure LV function

Exploratory Endpoints:

1) Evaluate the indices of glucose variability (mean, SD, CV, MACE, LBGI, AUC for hypoglycemia) during each intervention period

2) Assess the association between the indices of glucose variability and changes in measures of CAN parameters during each intervention phase

6.1 Recording of data

Case Report Forms (CRFs) for individual patients will be developed by the investigators and served as the source document. Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. The study staff will record all medical history, physical examination, safety laboratory assessment and all procedures involved during the study in CRF. Principle investigator will review, sign and date the results. The study staff will communicate with the patients regarding their results and appropriate follow-up and management. It is the sponsor- investigator's responsibility to ensure accuracy, completeness, legibility, and timeliness of the data reported. Data reported in the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies will be explained by the study staff. Any change or correction to a CRF will be dated, initialled, and explained by the study staff.

6.2 Data collection at enrollment and follow-up

The following data will be collected at enrollment periods (for each study drug period):

1. Vital signs: BP, weight, BMI, HR

2. Blood sample for safety laboratory assessments, glucose control and biomarker for cardiac function (CBCP, CMP including FBG, HbA1c, lipid panel and urine albumin assessment, BNP) (See Table 1)

3. ECGs for heart rate variability studies (LF, HF, LF/HF ratio, SDNN and RMSSD), cardiovascular autonomic reflex tests (E/I ration, Valsalva ratio, 30:15 and orthostatic BP) and RHR

4. Assessment of hypoglycemia by evaluating symptoms and downloading glucometers and glucose log sheets

During follow-up monitoring visits, we will assess hypoglycemia (symptoms, recordings) vital signs, any changes in their medication list, recording of adverse events, serious adverse events and compliance and tolerability of study medications.

At the end of each intervention period, we will repeat the same measures and procedures to obtain primary and secondary endpoints. Those include blood sample for biomarkers, HRV, and CARTs.

We will also evaluate the indices of glucose variability by using Freestyle Libre Pro CGM during each intervention phase in this cohort.

6.2.1 Enrollment procedures

All candidates will be selected from University of Michigan Health System (UMHS), which has a unified electronic medical records system (EPIC) that allows screening in real time for all patients seen at UMHS via best practice alerts. Currently there are ~ 25,000

patients with type 2 diabetes that are being seen in our system. In addition, we have access to the Diabetes Registry, an IRB approved registry of patients with diabetes who provided written consent to have their medical records screened to determine eligibility and to be contacted directly should they be eligible.

Once identified, the candidates will be contacted via phone or email and provided the information regarding the study. Following their review of the study, candidates who express interest in participation will be scheduled for a screening visit (visit 1) in the dedicated research space either within the outpatient clinics of the Division of Metabolism, Endocrinology and Diabetes (MEND) or at the Michigan Clinical Research Unit. (MCRU) (http://www.michr.umich.edu/services/mcru) depending on subjects preferences.

Once eligibility is confirmed, candidates will proceed to Visit 2-baseline visit within 4 weeks for randomization and dispensing study medication. Written instructions for use of the medication will be reviewed with and provided to the subject. All participants will be asked to monitor glucose in the morning and before dinner and record in the log book and meter.

6.2.2 Follow-up procedures

Follow-up monitoring visit will be scheduled every 4 weeks during intervention period. After randomization visit (Visit 2), the study staff will contact the subject within one week via phone to assess medication compliance and tolerance. Participants will be asked to record the number of doses taken every day on a log that will be provided. All participants will also be asked to monitor glucose in the morning and before dinner, and record those in the log book. Participants will be advised to bring the study medications, glucometers and glucose log books at each follow-up visit. Depending on glucose monitoring and their tolerability, the dose of study medications will be doubled in following visit (Visit 3). Subjects are to be reminded to return any unused study medication at their next visit.

6.3 Efficacy: NA

6.3.1 Efficacy variable: NA

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 (e.g., nausea, chest pain), signs (e.g.,

tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including washout period, 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 (i.e., 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

The investigators are responsible to perform periodic and special assessments for adverse events. All adverse events will be summarized and reported to the Institutional Review Board. The investigator and research staff will note all AEs reported by the subject after administration of dapagliflozin or glimepiride. All clinical complaints volunteered by, or elicited from, the subject during the study will be recorded in the appropriate section of the case report form for the study period indicated. AEs may include events that occur as a result of protocol-mandated procedures (e.g., events due to invasive procedures). We will only include non-invasive procedures such as HRV and CARTs for assessment of cardiovascular autonomic function. Therefore, AEs from protocol-mandated procedures are not likely expected other than minor skin irritation from electrodes. If any AE occurs, the subject will receive appropriate treatment and medical supervision and will be followed until the AE is stabilized or to a point where it is no longer clinically significant. As previously noted, all medical conditions and abnormal findings present before administration of the first dose of dapagliflozin or glimepiride will be recorded as concurrent illnesses or baseline symptoms.

Follow-up of unresolved adverse events: All AEs judged to be clinically significant, including clinically significant laboratory abnormalities, will be followed until resolution. The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Whether the AE is serious or not (that is, the intensity – mild, moderate or severe)
- Investigator causality rating against the Investigational Product or procedures (unlikely, possibly, probably, definitely)
- Action taken with regard to investigational product/procedure
- Adverse event caused subject's withdrawal from study (yes or no)
- Outcome (recovered, recovering, ongoing, fatal – see SAE).

In addition, the following variables will be collected for serious adverse events:

- 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.
- Date reported to IRB

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 a SAE.

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 glucose values and/or blood pressure values 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.

If deterioration in glucose concentration and/or blood pressure 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 (e.g., 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).

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.

Reporting of serious adverse events: Investigators must inform the FDA, via a Med Watch/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 AstraZeneca within 24 hours of events. A copy of the Med Watch/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 Med Watch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- 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.

The study staff will send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-1-302-886-4114 or email AEMailboxClinicalTrialTCS@astrazeneca.com within 24 hours of events.

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.

The investigator will contact the research pharmacist and request a copy of the randomization code to identify the subject with SAE for expedited reporting to IRB. The research pharmacist will indicate that the blind was broken on the Pharmacy Randomization Log and will document the date of the request, the name of the research personnel making the request, and the pharmacist's signature. The research coordinator will report the emergent event on the Adverse Event CRF and the unmasking event on the Unmasking Report CRF and then signed by the investigator.

All SAEs will also be reported to AstraZeneca within 24 hours, 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 (FDA) of the SAE.

6.4.4 Laboratory safety assessment

We will obtain the following safety laboratory samples at the screening visit before initiating of study medications and at the end of each study drug period: comprehensive metabolic panel including fasting blood glucose and CBC and platelets, urine albumin assessment and lipid profile.

At the screening visit (Visit 1), we will also obtain thyroid function test (TSH), urine pregnancy test and urine analysis.

For blood volume see Section 7.1.

6.4.5 Physical examination

Complete physical examination will be performed by either principle investigator or co-investigators. It will include general appearance, vital signs, and comprehensive systematic examinations including head and neck, cardiovascular exam, respiratory exam, gastroenterology exam, extremities, skin and neurology exam.

6.4.6 ECG

We will record baseline ECG while lying in all participants by using standard ECG monitoring device (Mortara Instrument, ELI 250).

6.4.6.1 Resting 12-lead ECG

12-lead ECG including I, II, III, aVR, aVL, aVF, V1 - V6 will be recorded with standardized devices and stored at the research facility. Morphology of waves at various leads, RR interval, corrected QT interval, and ST depression will be evaluated by the study investigators and recorded in the flow chart.

6.4.6.2 Real time display (telemetry): NA

6.4.7 Vital signs

It will include temperature, resting blood pressure, heart rate, weight in kg, height in cm, and calculated BMI.

6.4.7.1 Pulse and blood pressure

Systolic and diastolic blood pressure as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after approximately 5 minutes of rest in the seated position. The blood pressure measurement should be performed three times at each time point and the mean value of these measurements will be entered in the CRF.

6.4.7.2 Body temperature

All participants' body temperature will be recorded in CRF by using standard Welch Allyn Sure Temp Plus device.

6.4.8 Other safety assessments

Home Blood Glucose Monitoring

All patients will be provided with a glucometer for home blood glucose monitoring and supplies for use at home during 12-week intervention periods and wash-out period. Instruction on the proper use of the glucometer will be provided by the study staff. The patient will be asked to monitor glucose 2 times daily, in the morning and before dinner and to record the results of the glucose log book that will be included in the patient source document file.

6.5 Patient reported outcomes (PRO):

NA

6.5.1.1 <<Name of PRO method or questionnaire>>

NA

6.6 Pharmacokinetics

Blood samples for pharmacokinetic evaluation will not be collected before and after initiating of study medications in this crossover study. Primary outcomes include changes in measures of cardiovascular autonomic neuropathy among patients taking glimepiride or dapagliflozin.

The followings are the pharmacokinetic activities of FDA approved dapagliflozin and glimepiride.

Dapagliflozin

Absorption

Dapagliflozin is rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (Cmax) are usually attained within 2 hours after administration in the fasted state. The Cmax and AUC values increase proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food has relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreases dapagliflozin Cmax by up to 50% and prolonged Tmax by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in various disease states (e.g., renal or hepatic impairment).

Metabolism

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean plasma terminal half-life (t1/2) for dapagliflozin is 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-Oglucuronide accounted for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma, accounting for 42% (based on AUC [0-12 hour]) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounts for >5% of the total plasma radioactivity. Dapagliflozin 3-Oglucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism is a minor clearance pathway in humans.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After administration of 50 mg [14C]-dapagliflozin dose, 96% is recovered; 75% in urine and 21% in feces. In feces, approximately 15% of the dose is excreted as parent drug.

Glimepiride

Absorption

Studies with single oral doses of glimepiride in healthy subjects and with multiple oral doses in patients with type 2 diabetes showed peak drug concentrations (Cmax) 2 to 3 hours post-dose. When glimepiride was given with meals, the mean Cmax and AUC (area under the curve) were decreased by 8% and 9%, respectively. Glimepiride does not accumulate in serum following multiple dosing. The pharmacokinetics of glimepiride does not differ between healthy subjects and patients with type 2 diabetes. Clearance of glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetics. In healthy subjects, the intra- and inter-individual variabilities of glimepiride pharmacokinetic parameters were 15-23% and 24-29%, respectively.

Distribution

After intravenous dosing in healthy subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism

Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M2 is inactive. In animals, M1 possesses about one-third of the pharmacological activity of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans.

Excretion

When 14C-glimepiride was given orally to 3 healthy male subjects, approximately 60% of the total radioactivity was recovered in the urine in 7 days. M1 and M2 accounted for 80-90% of the radioactivity recovered in the urine. The ratio of M1 to M2 in the urine was approximately 3:2 in two subjects and 4:1 in one subject. Approximately 40% of the total radioactivity was recovered in feces. M1 and M2 accounted for about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in feces. No parent drug was recovered from urine or feces. After intravenous dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed.

6.6.1 Collection of samples

NA

6.6.2 Determination of drug concentration: NA

Determination of drug concentration will not be investigated in this study.

6.7 Pharmacodynamics

No pharmacodynamics parameters will be determined in this study.

6.7.1 Collection of pharmacodynamics markers:

NA

6.8 Pharmacogenetics: NA

No pharmacogenetic samples will be investigated in this study.

6.8.1 Collection of pharmacogenetic samples: NA

6.9 Health economics

This study is a pilot crossover clinical trial comparing 12 weeks of glycemic intervention on measures of cardiovascular autonomic neuropathy in patients with type 2 diabetes. The duration of the study is quite short. Therefore, it is likely that this study won't be able to offer health economics parameters. However, we may consider performing analysis of glucose control and risk of hypoglycemic in study patients.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The study staff will collect 4 tubes of blood samples in screening visit (visit 1), visit 5, and visit 9. We will also collect 1 tube of blood sample at visit 6. Each tube contains 6ml blood sample (each tube 6 ml = 1 teaspoon). A total of 78 ml (13 teaspoons) of blood per subject will be taken for the entire study.

7.2 Handling, storage and destruction of biological samples

We will obtain all safety laboratory samples after overnight fasting at screening visit before initiating of study medications and at the end of each intervention period. Sample will be marked using subject unique study ID number. Study coordinator will keep separate list that links personal identity to ID number until all data have been analyzed and verified. All safety laboratory including HbA1c, liver transaminases (AST, ALT), alkaline phosphatase, serum creatinine, hematocrit, hemoglobin, red blood cell count, white blood cell count, platelet count, electrolytes (sodium, potassium, chloride, bicarbonate, Chloride, Calcium, bilirubin, Urea, total protein, albumin, FBG), lipid panel (Total cholesterol, Triglycerides, HDL, LDL) will be processed immediately after collection. Then we will dispose those blood samples to the container labeled as Biohazard through Hazardous Materials Management (HMM) for the collection of liquid biohazardous waste.

7.2.1 Pharmacokinetic and/or pharmacodynamics samples

No pharmacokinetic and pharmacodynamics samples will be collected during the study

7.2.2 Pharmacogenetic samples:

No pharmacogenetics samples will be collected during the study

7.3 Labeling and shipment of biohazard samples

NA

7.4 Chain of custody of biological samples

NA

7.5 Withdrawal of informed consent for donated biological samples

A subject may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If the subject withdraws consent, no further evaluations should be performed and no attempts should be made to collect additional data. We will not process stored biological samples of such particular subject. It will be disposed safely through HMM.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

8.2 Ethics and regulatory review

Institutional Review Board (IRB)

It is the responsibility of the investigator to obtain prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB. All correspondence with the IRB should be retained in the Investigator File.

8.3 Informed consent

The informed consent form must be agreed to by the Protocol Committee and the IRB and must be in compliance with ICH Good Clinical Practice Guidelines, local regulatory requirements, and legal requirements.

The investigator must ensure that each trial subject, or her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The investigator will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The informed consent form used in this trial, and any changes made during the course of the trial, must be prospectively approved by the IRB before use. The investigator will retain a copy of each subject's signed consent form.

Study records with the study participant's information for internal use at the clinical sites will be secured at the study site during the study. At the end of the study, all records will continue to be kept in a secure location. There are no plans to destroy the records.

Study participant data, which is for reporting purposes, will be stored at the Coordinating Center. Data will identify participants by the unique study identification number. The study data entry and study management systems used by clinical sites and by Coordinating Center research staff will be a secured, password protected computer.

8.4 Changes to the protocol and informed consent form

NA

8.5 Audits and inspections

Audits and inspections may be pursued by the Michigan Institute of Clinical Research as part of implementing quality assurance of the study trial and the time interval of audits will be scheduled based on discretion of these parties.

9. STUDY MANAGEMENT

The principle investigator and co-investigators will be responsible for oversight of all aspects of the study. The study will be conducted according to ICH Good Clinical Practice Guidelines and in accordance with University of Michigan Health System (UMHS) policies.

9.1 Training of study site personnel

A delegation log of research personnel will be generated. The study staff will be trained for the following study procedures and certified by principle investigator:

- Heart rate variability (HRV) studies,
- Cardiovascular reflex tests (CARTs)
- Freestyle Libre Pro CGM

The efficiency of training of study staff will be periodically assessed by principle investigator. All study staff should be certified for Program for Education and Evaluation in Responsible Research and Scholarship (PEERRS) as part of regulation by Michigan Institutes

for clinical and Heath research (MICHR). These courses provide training required per university, state, and federal regulations regarding responsible conduct of research (RCR). The study staff will be also trained to report all un-anticipated events, deviations, and AEs to IRBMED.

9.2 Monitoring of the study

9.2.1 Source data

Protocol for Case Report Form (CRF) will be developed and served as the source document. Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. We will record all medical history, physical examination, safety laboratory assessment and all procedures involved during the study in CRF. It is the investigator's responsibility to ensure completion and to review and approve all CRFs. Additional source data will be in patients' medical record in electronic medical record aka Michart. Michart will also be used as source document. Outside medical record may also be requested for source document.

9.3 Study timetable and end of study

Projected study timelines are as the following:

Research Agreement executed: Oct 30, 2016

Projected IRB/IEC approval: Nov 30, 2016

First Subject In: Dec 30, 2016

50% Enrollment: Sep 30, 2017

Last Subject In (100% enrollment): Jun 30, 2018

Last Subject Last Visit (Treatment end): Dec 30, 2018

Publication: Mar 30, 2019

10. DATA MANAGEMENT

Case Report Forms / Electronic Data Record

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial.

A CRF is required and should be completed for each included subject. It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve

to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Subject source documents are the physician's subject records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, the investigator must prospectively document which items will be recorded in the source documents and for which items the CRF will stand as the source document.

11. EVALUATION AND CALCULATION OF VARIABLES

NA

11.1 Calculation or derivation of efficacy variable(s)

NA

11.2 Calculation or derivation of safety variable(s)

NA

11.2.1 Other significant adverse events (OAE)

NA

11.3 Calculation or derivation of patient reported outcome variables

NA

11.4 Calculation or derivation of pharmacokinetic variables

NA

11.5 Calculation or derivation of pharmacodynamic variable(s)

NA

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

NA

11.5.2 Population analysis of pharmacokinetic/pharmacodynamic variables

NA

11.6 Calculation or derivation of pharmacogenetic variables

NA

11.7 Calculation or derivation of health economic variables

NA

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

The primary efficacy analysis set will be based on a pharmacodynamic set such that subjects must have non-missing observations of study endpoints in both periods. A secondary analysis will be performed on the intent-to-treat (ITT) set which includes all patients who receive at least 1 dose of treatment.

12.1.2 Safety analysis set

All patients will be evaluable for toxicity from the time of their first treatment. All safety laboratory measurements (see section 6.4.5) and any reported or observed AEs (see section 6.4.3) will be documented in source document.

12.2 Methods of statistical analyses

The primary objective of this trial is to compare the change in the LF: HF ratio from baseline to 12 weeks for patients on dapaglifozin versus glimepiride.

The mean change in LF: HF ratio for each drug from baseline to 12 weeks will be reported with the corresponding 95% confidence interval. The mean difference between drugs of changes from baseline to 12 weeks and the corresponding 95% confidence interval will also be reported. The change from baseline to 12 weeks within each period (between drugs) will be compared within patients using a two-sided t-test (applying transformations where appropriate; using the pharmacodynamics set of subjects). This analysis will be repeated using the ITT set of subjects. If there is chance within-subject or between-subject imbalance in baseline measures (such as glucose control, BMI and age), we will use the ANCOVA method including those unbalanced covariates to improve precision (Metcalfe, Statistics in Medicine, The analysis of cross-over trials with baseline measurements, 2010).

A corresponding primary analysis to the t-test controlling for possible sequence and period effects includes a linear mixed effects model (also known as random effects model; applying transformations where appropriate) with outcome of the change in LF: HF ratio from baseline to 12 weeks. This model assesses the difference between drugs by accounting for a

random effect for subject (nested within sequence) and fixed effects for treatment, sequence, and period.

We will additionally explore differences between the drugs over time using all of the data measured at baseline, 4, 8 and 12 weeks with a linear mixed model. The outcome will be the change from baseline at 4, 8 and 12 weeks. The model will include a random term for subject nested within sequence and fixed effects for treatment, sequence, visit, period, and interaction terms for visit by treatment. The interaction terms for visit by treatment provide estimates of treatment effects at each visit. An unstructured variance/covariance matrix will be used.

All secondary endpoints will be similarly compared where each endpoint for each drug will be measured at baseline and 12 weeks and the difference within each drug will be compared within patients using a two-sided t-test (applying transformations where appropriate). Similar to the analysis for the main outcome, linear mixed effect models with an unstructured variance/covariance matrix and outcomes of changes from baseline at 4, 8, and 12 weeks will assess changes over time for each outcome. The mixed effects models will include a random effect for patients nested within sequence and fixed effects for treatment, sequence, visit, period and the interaction between treatment and visit.

Associations between the indices of glucose variability and changes in measures of HRV during each intervention will be analyzed using paired t-tests or Wilcoxon signed rank test (if normality assumption is violated). Effect sizes will be estimated with 95% confidence intervals of the associations between glucose variability and changes in measures of HRV within each intervention using linear regression (applying transformations when necessary). If period effects are found from our primary analysis, we will control for the period in which the drug was given within the model. The interaction between drug and glucose variability on the changes in measures of HRV will be explored using a generalized estimating equations (using an unstructured working correlation matrix since we only have 2 observations per person). We will not control for multiple comparisons and expect results to be validated in a future independent cohort.

12.2.1 Interim analyses

No interim analysis is planned. The study medications, dapagliflozin and glimepiride, are FDA approved drugs for treatment of type 2 diabetes. They are very effective in lowering glucose. There is no harm in continuing treatment for the entire study period due to their safety profile as mentioned above (see section 1.4 and 13).

12.3 Determination of sample size

We assume there are no carryover effect and no interactions between patients, treatments, and time period. For each patient in each period (on each drug), the LF: HF ratio will be measured at baseline and at 12 weeks. The primary outcome will be the difference between periods (drugs) in the differences from baseline to 12 weeks of the LF: HF ratio (i.e. [LF: HF sulfonylurea, week12 – LF: HF sulfonylurea, baseline] – [LF: HF dapagliflozin,

week12 – LF: HF dapagliflozin, baseline]). Based on previous studies, we have found the LF: HF ratio to have a mean of 3.4 (SD=2.1) for those with T2D. Assuming a similar within person standard deviation (2.1) of the difference of the differences in the LF: HF ratio from baseline to 12 weeks, we have 80% power with 38 patients to find a difference between the two drugs in the differences in LF: HF ratios of 1.4 using a two-sided (paired) t-test at the 0.05 significance level (sample size from applet available at http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html). Expecting 10% of the subjects to not complete the entire study, we plan to enroll 45 patients.

12.4 Data monitoring committee

A Data and Safety Monitoring Board (DSMB) will oversee this study. This is the single center cross-over pilot study using on-label study medications. Therefore, we feel that composing DSMB with an endocrinologist and a biostatistician would be appropriate to monitor the study. Members of the DSMB are independent of the study investigators and study biostatistician. The DSMB will meet every six months. During the DMSB's meetings, the team will discuss matters related to: enrollment rate relative to expectations; characteristics of participants; safety of study participants (SAE and AE reporting); adherence to protocol (protocol deviations); completeness, validity and integrity of study data; and retention of study participants.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

Given the mechanistic nature of the study drug, dapagliflozin, the common side effects are urinary tract infection (UTI) and genital mycotic infection. Those patients who developed infections will be managed according to standard care and guidelines. Baseline urinary analysis (UA) will be collected before starting any study medications. In any case of suspect UTI, UA will be collected. If positive urine analysis, then we will proceed with urine culture and treat the patient accordingly to bacterial growth in the urine culture. If negative UA, we will not proceed with midstream urine culture.

If the patient has abnormal ECG, the study investigator will ask the prior documented ECG report from patient's primary care provider or endocrinologist and repeat the ECG. If the patient is symptomatic, then patient will be sent to emergency department for further urgent evaluation of coronary artery disease. The study medication will be discontinued. If asymptomatic, then the investigators will ask the prior ECG report and repeat ECG in the same visit. If similar findings compared to the old one, then he will be monitored conservatively. If significant changes from prior ECG, then he will be referred to the cardiologist for further evaluation upon the investigator's discretion.

13.1 Overdose

Orally administrated dapagliflozin has been shown to be safe and well tolerated in healthy subjects at single doses up to 500 mg [50 times the maximum recommended human dose (MRHD)]. These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose) with no reports of dehydration, hypotension, or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) of dapagliflozin were administered for 2 weeks in healthy subjects and type 2 diabetes patients, the incidence of hypoglycemia for subjects administered dapagliflozin was slightly higher than placebo and was not dose related. Rates of adverse events including dehydration or hypotension for patients treated with dapagliflozin were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters including serum electrolytes and biomarkers of renal function. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

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

An over dosage of glimepiride, as with other sulfonylureas, can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with

glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery.

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

13.2 Pregnancy

All female reproductive aged participants will be asked to use a definitive form of contraception before enrolling in the study. However, pregnancy might occur in the study period. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy and stop the study medication. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. All outcomes of pregnancy should be reported to AstraZeneca.

13.2.1 Maternal exposure

Dapagliflozin is pregnancy category drug C. Based on the results of reproductive and developmental toxicity studies in animals, dapagliflozin doses > 137 MRHD may affect renal development and skeletal malformation and maturation.

Glimepiride is pregnancy category drug C. There are no adequate and well-controlled studies in pregnant women. In animal studies there was no increase in congenital anomalies, but an increase in fetal deaths occurred in rats and rabbits at glimepiride doses 50 times (rats) and 0.1 times (rabbits) the maximum recommended human dose (based on body surface area).

As soon as we learn that a female subject has been pregnant, we will stop the study medication immediately. We will report this to AstraZeneca and IRBMED immediately. Patient will be asked to follow with her Obstetrician closely. We will also follow the pregnancy outcomes and report this to AstraZeneca.

13.2.2 Paternal exposure

Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples ≤1708 times and 998 times the maximum recommended human dose in males and females, respectively.

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Therefore, male subjects may have children while on study medications.

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Documentation of the Informed Consent Process for Onsite Subject File

Protocol No.:HUM00121107
Study Title/PI: Dapagliflozin and Measures of Cardiovascular Autonomic Function in Patients with Type 2 Diabetes (T2D)
Rodica Pop-Busui, Ph.D, M.D.
Subject ID: _____
Consent Obtained by: _____
Date of Consent: _____

	15. CHECK ALL THAT APPLY
☐	The subject meets all eligibility requirements.
☐	Discussed, explained and reviewed the consent form with subject. ❑ Verbal consent was obtained (per IRB approved consent process) ❑ Surrogate consent was obtained (per IRB approved consent process)
☐	All of the subject's questions were answered/concerns addressed. (document multiple subject contacts below) ❑ Subject did not have any questions/concerns
☐	Subject was given time to review the consent form and to discuss participation in this study with family members/others.
☐	The subject has agreed to participate in the study and signed/dated a valid consent form *prior to the start of any study procedures*.
☐	The consent process was witnessed by a third party (if applicable). Witnessed by:
☐	A copy of the signed and dated consent form was given to the subject.
☐	A copy of the signed and dated consent form was placed in the medical record.
☐	A copy of the signed and dated consent form was placed in the research record.

Signature/Initials:	Date:

MEDICAL HISTORY WORKSHEET

DATE _____

SUBJECT ID _____ STAFF INITIALS _____

Record all past and/or concomitant medical conditions or surgeries. Record only one condition or surgery per line using the codes provided in the table. When recording a condition and surgery related to that condition use one line for the condition and one line for the surgery.

01 Head, Eye, Ear, Nose, Throat	06 Musculoskeletal	11 Psychiatric
02 Respiratory	07 Neurological	12 Allergy
03 Cardiovascular	08 Endocrine/Metabolic	91 Other
04 Gastrointestinal	09 Blood/Lymphatic	
05 Genitourinary	10 Dermatologic	

Code	**Condition/Disease (one item per line)**	**Start Date dd/mmm/yyyy**	**Current / Resolved**
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved

			☐ Current ☐ Resolved
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved

PHYSICAL EXAMINATION WORKSHEET

DATE _____

SUBJECT ID _____ STAFF INITIALS _____

Please complete checklist and describe any abnormalities.

	Normal	Abnormal	Not done	
Eyes (including fundoscopy)	☐	☐	☐	Retinopathy, macular degeneration
Other				_____
Cardiovascular	☐	☐	☐	Arrhythmia, murmur
Other				_____
Extremities	☐	☐	☐	Amputation, tenderness, edema
Pulses: 1+ / 2+ / 3+ / 4+				
Other				_____
Lymph Nodes	☐	☐	☐	Swelling
Other				_____
Pulmonary	☐	☐	☐	Decreased breath sounds
Other				_____
Skin	☐	☐	☐	Red or purple painful rash, scar,eczema, psoriasis, ulcer, excessive bruising
Other				_____
Gastrointestinal	☐	☐	☐	Ascites, abdominal mass, Organomegaly, stoma
Other				_____
Musculoskeletal	☐	☐	☐	Joint pain stiffness or swelling, Muscle pain or weakness, difficulty

walking or moving

Other _____

Neurological ☐ ☐ ☐ Abnormal reflexes (hypo/ hyperreflexia), decreased sensation cranial nerves (abnormal – specify)

Other _____

Reflexes ☐ ☐ ☐ _____

Other, specify:

_____

Is participant having any side effects from study meds? Yes ☐ No ☐

If yes, specify:

_____

NOTE: If participant has side effects, complete AE worksheet and SAE worksheet (if necessary).

If this is a screening Physical Exam, is participant eligible based in this exam?

Yes ☐ No ☐ N/A ☐ If no, explain:

_____
_____
_____
_____
_____

Physician's Name (printed):_____

Physician's Signature: _____

Medical History Changes

Subject ID: _____ Date: _____

Visit: _____

Was there a change in your medical or surgical history? ☐ Yes ☐ No

If yes, describe:_____
_____
_____
_____

Was there a change in your current medications? ☐ Yes ☐ No

If yes, describe: _____
_____
_____
_____

Study **Title: DAPA-CAN HUM00121107** **Staff Initials:** _____

Subject ID: _____

CONCOMITANT MEDICATIONS WORKSHEET

Is the participant taken any concomitant medications at screening or during the prior 3 months					☐ **No** ☐ **Yes,** Complete below		
Medication (Record Generic or trade name)	Reason for use (Medical History diagnosis or other reason, e.g. Prophylaxis)	Dose and units	**Frequency**	**Route**	**Start Date** (DD/MMM/YYYY)	**Stop Date** (DD//MMM /YYY)	**Or tick if ongoing at Screening Visit**
1.					____/_____/_____	____/_____/_____	☐
2.					____/_____/_____	____/_____/_____	☐
3.					____/_____/_____	____/_____/_____	☐
4.					____/_____/_____	____/_____/_____	☐
5.					____/_____/_____	____/_____/_____	☐
6.					____/_____/_____	____/_____/_____	☐
7.					____/_____/_____	____/_____/_____	☐
8.					____/_____/_____	____/_____/_____	☐
9.					____/_____/_____	____/_____/_____	☐
10.					____/_____/_____	____/_____/_____	☐

DATE _ _/_ _/_ _ _ _
mo day yr

SUBJECT ID _ _ _ STAFF INITIALS _ _ _

Cardiovascular Autonomic Neuropathy Testing Worksheet

PREPAREDNESS FOR TESTING (If YES is answered to any of the questions below, patient is ineligible for CAN testing today. Reschedule the patient for testing another day and discard this form.)	
	No Yes
1. Any food since in the past 12 hours?	(1) (2)
2. Any liquids in the past 12 hours? (except water)	(1) (2)
3. Any caffeine in the past 12 hours?	(1) (2)
4. Any medication in the past 12 hours (excluding basal pump insulin)?	(1) (2)
5. Any over-the-counter drugs in the past 12 hours (aspirin, antihistamines, nasal spray, etc.)	(1) (2)
6. Any alcohol in the last 24 hours	(1) (2)
7. Any tobacco in the past 12 hours?	(1) (2)
8. Any vigorous exercise in the last 24 hours? (Any exercise not part of patient's daily routine, i.e., routine jogging O.K., but marathon running is not. NO exercise morning of test.)	(1) (2)
9. Any emotional upset in the last 24 hours" (Depression, crying episodes, anxiety from personal trauma	(1) (2)
10. Acute illness in last 48 hours? (cold, flu, measles, etc.).	(1) (2)
11. Any hypoglycemic episodes since midnight?	(1) (2)
12 a) Fasting blood sugar value (finger stick method O.K.)	___ ___ ___ mg/dl
b) Below 50 or signs or symptoms of hypoglycemia?	(1) (2)
VITAL SIGNS	

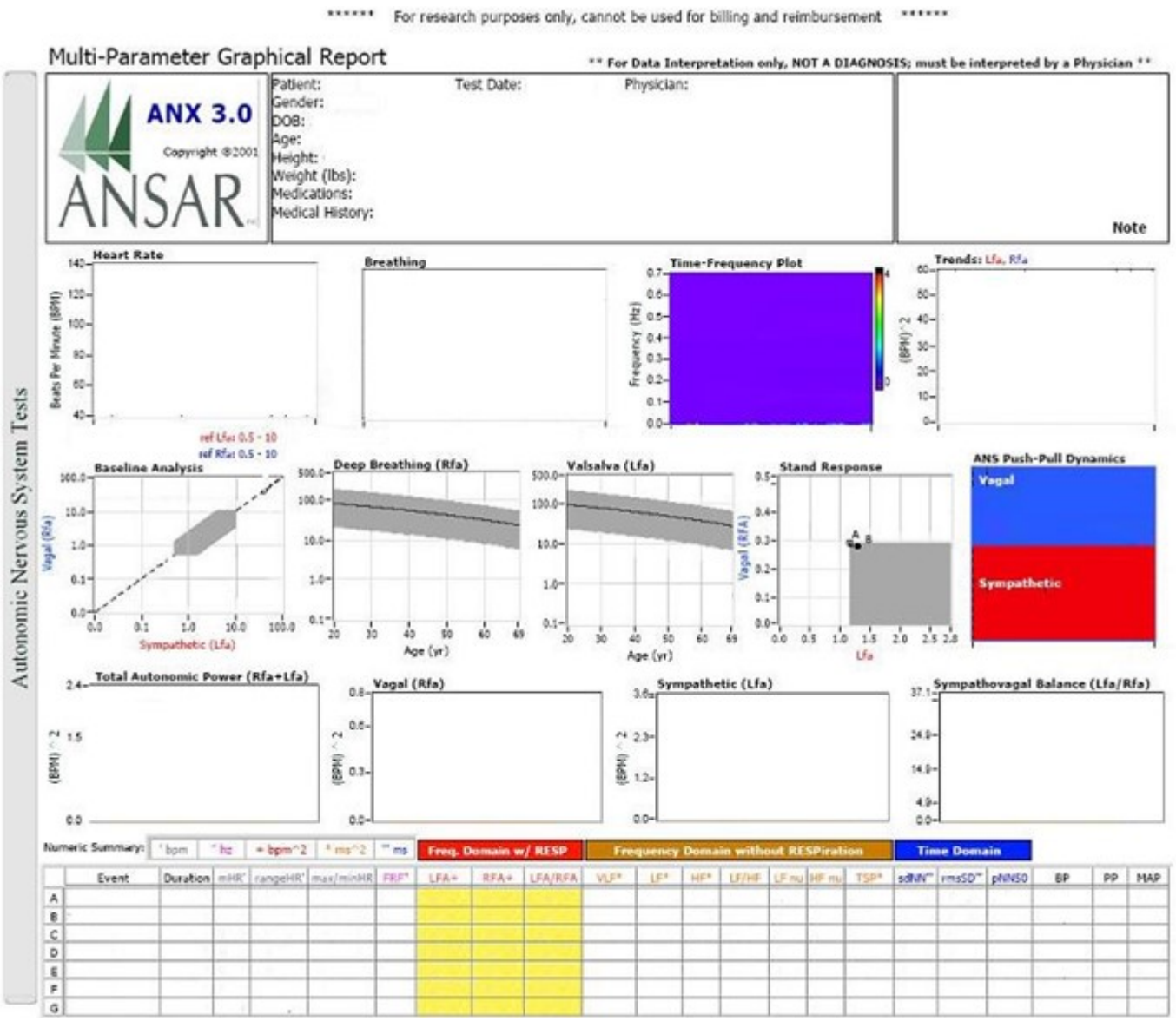
1. Height 2. Weight	___ ___ ___ . ___(cm) ___ ___ ___ . ___(kg)
3. BP 4. Pulse	__ __ __ / __ __mmHg ___ ___ ___ BPM
List any medications taken in the last 48 hours:	

Form completed by:_____

DATE __ __/__ __/__ __ __ __
mo day yr

SUBJECT ID __ __ __ STAFF INITIALS __ __ __

Heart Rate Variability Test Report



Technician's Signature:_____ **Date:**_____

Physician's Signature:_____ **Date:**_____

Adverse Event Monitoring

Subject ID: _____

Date: _____

Visit: ____

Was there any new or worsening adverse events reported?

- ☐ Yes, new event(s)
- ☐ Yes, worsening event(s)
- ☐ Yes, both
- ☐ No

Number of new or worsening adverse events: _____

Were any of the following events reported (check all that apply)?

- ☐ Urinary Tract Infection
- ☐ Genital Infection
- ☐ Hypotension
- ☐ Dehydration
- ☐ DKA
- ☐ Other

If other, describe:

_____

*If there was a new or worsening adverse event, fill out a corresponding AE form for each event.

Completed By: _____ Date: _____

Adverse Event Form

Subject ID: _____

AE Number: AE __ __

Description of AE:
_____
_____

Date this Report Opened: _____

Date this Report Closed: _____

Most recently completed subject visit number (if event is reported in context of current visit, record today's visit number): _____

Date Adverse Event Started: _____
(can be approximate or unsure)

Date that the Study Staff Learned of the Event: _____

Date Adverse Event Abated: _____
(can be approximate or unsure, leave blank until abated)

☐ Check if ongoing at conclusion of study

Indicate PI initial level of severity using the scale below:

☐ 1 - Mild AE - No treatment needed
☐ 2 - Moderate AE - Resolved with treatment
☐ 3 - Severe AE - Inability to carry on normal activities, required professional medical attention.
☐ 4 - Life-threatening or disabling AE
☐ 5 - Fatal AE

Indicate the final PI level of severity using the scale below:

☐ 1 - Mild AE - No treatment needed
☐ 2 - Moderate AE - Resolved with treatment
☐ 3 - Severe AE - Inability to carry on normal activities, required professional medical attention.
☐ 4 - Life-threatening or disabling AE
☐ 5 - Fatal AE

Indicate the PI initially relation to study participation.

☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Unrelated

Indicate the PI final relation to study participation.

☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Unrelated

Was the event expected? ☐ Yes ☐ No

What action was taken for the event reported (check all that apply)?

☐ No action taken

☐ Medication Prescribed

☐ Non-Drug Treatment Prescribed (e.g., physical therapy)

☐ Study Medication Dose Reduced

☐ Study Medication Stopped

☐ Outpatient Medical Visit

☐ Urgent Care Visit

☐ Emergency Room Visit

☐ Hospitalization

☐ Other

If other, describe: _____

Was medication stopped or reduced? ☐ Yes ☐ No

Date dose was stopped or reduced: _____

Did the adverse event abate after stopping/reducing study medication?
☐ Yes ☐ No

If yes, has the study medication dose increased or restarted?
☐ Yes ☐ No

Date medication was increased or restarted: _____

Was AE submitted to UM IRB? ☐ Yes ☐ No ☐ Pending yearly submission

Date of Submission: _____

Did this event meet the definition of a serious adverse event? ☐Yes ☐No

*If this adverse event meet the definition of a serious adverse event, complete a serious adverse event form.

Comments:

Complete By: _____ Date: _____

Principal Investigator Signature: _____ Date: _____

Serious Adverse Event Form

Subject ID: _____

SAE Number: SAE __ __

Description of Serious Adverse Event: _____

_____

Date this Report Opened: _____

Date this Report Closed: _____

Most recently completed subject visit number (if event is reported in context of current visit, record today's visit number): _____

Date Serious Adverse Event Occurred/Started: _____

Date that the Study Staff Learned of the Event: _____

Date Serious Adverse Event Abated: _____
(can be approximate or unsure, leave blank until abated)

☐ Check if ongoing at conclusion of study

Is this a Death? ☐ Yes ☐ No

Date of Death: _____

Location of Death: _____

Probable Cause of Death: _____

Is this a Life-Threatening Event? ☐ Yes ☐ No

Did the event result in inpatient hospitalization or prolongation of existing hospitalization?

☐ Yes ☐ No

If yes, number of days in hospital: _____

Did the event result in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions?

☐ Yes ☐ No

Is the event a pregnancy resulting in a congenital anomaly or birth defect?

☐ Yes ☐ No

Was this a serious event in the judgment of the investigator that required medical or surgical intervention to prevent death, hospitalization of life-threatening outcomes?

☐ Yes ☐ No

Was the event due to an overdose of study medication?

☐ Yes ☐ No

Indicate the PI initially relation to study participation.

☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Unrelated

Indicate the PI final relation to study participation.

☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Unrelated

Was the Event Expected? ☐ Yes ☐ No

Indicate PI initial level of severity using the scale below:

☐ 1 - Mild AE - No treatment needed
☐ 2 - Moderate AE - Resolved with treatment
☐ 3 - Severe AE - Inability to carry on normal activities, required professional medical attention.
☐ 4 - Life-threatening or disabling AE
☐ 5 - Fatal AE

Indicate the final PI level of severity using the scale below:

☐ 1 - Mild AE - No treatment needed
☐ 2 - Moderate AE - Resolved with treatment
☐ 3 - Severe AE - Inability to carry on normal activities, required professional medical attention.
☐ 4 - Life-threatening or disabling AE
☐ 5 - Fatal AE

What action was taken for the event reported (check all that apply)?

☐ No action taken

☐ Medication Prescribed

☐ Non-Drug Treatment Prescribed (e.g., physical therapy)

☐ Study Medication Dose Reduced

☐ Study Medication Stopped

☐ Outpatient Medical Visit

☐ Urgent Care Visit

☐ Emergency Room Visit

☐ Hospitalization

☐ Other

If other, describe: _____

Was medication stopped or reduced? ☐ Yes ☐ No

Date dose was stopped or reduced: _____

Did the event abate after stopping/reducing study medication? ☐ ☐ Yes No

If yes, has the study medication dose increased or restarted?
☐Yes ☐No

Date medication was increased or restarted: _____

Was SAE submitted to UM IRB? ☐Yes ☐ No

Date of Submission: _____

Comments:

Completed by: _____ Date: _____

Principal Investigator Signature: _____ Date: _____

DATE __ __/__ __/__ __ __ __
mo day yr

SUBJECT ID _ _ _ STAFF INITIALS _ _ _

INSTRUCTIONS FOR HEART RATE VARIABILITY (HRV) TESTING

CAN testing is done to evaluate the nerves that help to regulate heart rate and blood pressure.

Many factors can affect CAN test results, so for accurate testing, we ask that you read and follow these instructions carefully and completely. As always, if you have any questions or concerns about these, please contact us so that we can discuss them.

1. FAST FOR 12 HOURS PRIOR TO TESTING and NO CAFFEINE 12 HOURS prior to testing. You should have nothing to eat or drink except water for at least 12 hours before your appointment. Water is fine, but other beverages, even if they are decaffeinated, are to be avoided.

2. AVOID LOW BLOOD SUGAR. Low blood sugar reactions can greatly affect CAN test results, so it is very important to avoid lows, even mild low blood sugar reactions in the 12 hours before the test. TAKE STEPS TO PREVENT LOW BLOOD SUGAR. You may need to eat something before you go to bed, and / or reduce your evening or overnight insulin to prevent going low. If you need help making insulin dose adjustments, please contact Dr. Pop-Busui AT 734-647-9809 OR ASK OPERATOR (734-936-6267) TO PAGE HER.

3. DO NOT TAKE ANY MEDICATIONS for 12 hours prior to the test. This includes prescription and over the counter medications. Bring your medications (including your insulin) with you so that you can take them as soon as the testing is done. IF YOU HAVE QUESTIONS ABOUT THIS, OR CONCERNS ABOUT SPECIFIC MEDICATIONS THAT YOU TAKE THAT ARE ON A VERY SPECIFIC SCHEDULE PLEASE CONTACT DR. POP-BUSUI PRIOR TO YOUR TEST.

4. NO ALCOHOL for 24 hours before the test. Alcohol can interfere with the function of autonomic nerves, so any alcohol consumed in the 24 hours prior to your test may lead to invalid results.

5. NO VIGOROUS EXERCISE for 24 hours prior to the test AND NO EXERCISE ON MORNING OF TEST. Exercise that is part of your daily routine is fine in the 24 hours prior to testing (for example – routine jogging is okay, but running a marathon the day before testing is not – unless you run marathons on a daily basis).

6. SIGNIFICANT EMOTIONAL UPSET within 24 hours of testing can also lead to invalid test results. If something comes up the day before testing that is very upsetting, please call to discuss rescheduling the appointment.

7. ANY ACUTE ILLNESS IN THE 48 HOURS PRIOR TO TESTING (such as colds, flu's, dental work) may affect test results. If you are sick or feeling unwell, please call and we can discuss whether or not we should reschedule this test.

8. NO SMOKING FOR AT LEAST 12 HOURS PRIOR TO TESTING. If you do smoke, please do not have any cigarettes/cigars for at least the eight hours prior to testing.

Finally, please bring your blood glucose monitor with you. I will be asking you to check your blood sugar just before testing starts. Thank you and please call or email if you have any questions about the CAN testing or these instructions.

Dr. Rodica Pop-Busui: (734) 647-9809; rpbusui@umich.edu

Dr. Lynn Ang: (734) 232-8058; angly@med.umich.edu

CASE REPORT FORM: SCREENING VISIT (VISIT 1)

SUBJECT ID: _____

VISIT DATE: _____

CONSENT SIGNED: ☐

Eligibility Checklist: INCLUSION CRITERIA and EXCLUSION CRITERIA

Inclusion Criteria – All must be checked to be in study

- ☐ Type 2 diabetes
- ☐ At least 18 Years of age
- ☐ BMI ≤45 kg/m2
- ☐ Background metformin monotherapy
- ☐ Willing and able to take an oral (by mouth) medication once per day for 2 periods
- ☐ WOMEN using an appropriate method of contraception during the course of the study (hormonal, IUD, or diaphragm).

EXCLUSION CRITERIA – If any are checked, cannot be in the study

- ☐ History of recurrent urinary tract infections
- ☐ Current participation or participation within the last three months in an experimental drug study.
- ☐ Fungal infection, especially genital infections
- ☐ Severe low blood pressure
- ☐ History of unexplained microscopic or gross hematuria (blood in your urine) (confirmed by follow-up)
- ☐ Allergy to and/or have evidenced sensitivity (i.e. swelling, skin rashes) to the study medications (brand names: Farxiga and Amaryl) or other SGLT2 inhibitors (i.e. Jardiance, Invokana)
- ☐ History of diabetic ketoacidosis
- ☐ If you had a cardiovascular event (such as surgery, angioplasty, heart attack, stroke, peripheral artery disease) in the last three months.
- ☐ Severe kidney disease or rapidly progressing kidney disease

- ☐ Any clinical conditions that could interfere with the cardiovascular autonomic function and heart rate variability testing (arrhythmias)
- ☐ Severe liver insufficiency and/or significant abnormal liver function
- ☐ History of cancer other than basal cell carcinoma and/or treatment for cancer within the last five years
- ☐ History of drug or alcohol abuse in prior 5 years.
- ☐ History of pancreas, kidney or liver transplant
- ☐ Allergy to sulfa drugs
- ☐ Class III or IV congestive heart failure

Completed by: _____

Participant Information Survey

HAS THE PATIENT PROVIDED SIGNED INFORMED CONSENT TO PARTICIPATE IN THIS RESEARCH STUDY? ☐ Yes ☐ No

UMHS MRN: _____

Pronoun: _____

First Name: _____

Last Name: _____

Date of Birth: ☐☐ / ☐☐ / ☐☐☐☐

Gender at Birth: ☐ Male ☐ Female

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown / Not Reported

Race: ☐ American Indian/Alaska

☐ Asian

☐ Native Hawaiian or Other Pacific Islander

☐ Black or African American

☐ White

☐ More than One Race

☐ Unknown / Not Reported

Date of Diabetes Diagnosis: ☐☐ / ☐☐☐☐ (MM-YYYY)

Address, Street, City, State, ZIP:
_____

Primary Phone Number: _____

Secondary Phone Number: _____

Email Address: _____

Secondary Email Address: _____

Completed By: _____ Date: _____

Visit 1 Overview and Screening Disposition

SUBJECT ID: _____

Date: _____

Weight (kgs): _____ Height (inches): _____

Pulse (seated): _____ Blood Pressure (seated): _____

Assessments

- ☐ Informed Consent — Performed by: _____
- ☐ Medical History and Physical Examination — Performed by: _____
- ☐ ECG — Performed by: _____
- ☐ Laboratory Measures — Performed by: _____

Urine Pregnancy Test Completed for Women and Result:

☐ Negative ☐ Positive ☐ Not Done ☐ Not Applicable

DISPOSITION: ☐ Eligible ☐ Not Eligible

If eligible, schedule a baseline visit to occur within 30 days.

BASELINE VISIT DATE: _____

Comments:

Signature of Coordinator: _____ Date: _____

Visit 2 Overview

SUBJECT ID: _____

Date: _____

Weight (kgs): _____ Blood Pressure (seated): _____

Pulse (seated): _____ Resting HR (supine from HRV): _____

Height (inches):_____ _____

Assessments

- ☐ HRV Testing — Performed by:_____
- ☐ CARTs Testing — Performed by: _____
- ☐ Assess Hypoglycemia — Performed by: _____
- ☐ Medication Dispensing — Performed by: _____
- ☐ Adverse Events Monitoring — Performed by: _____

Urine Pregnancy Test Completed for Women and Result:

☐ Negative ☐ Positive ☐ Not Done ☐ Not Applicable

VISIT 3 Scheduled for: _____

Comments:

Signature of Coordinator: _____ Date: _____

Visit 3 Overview

SUBJECT ID: _____Date: _____

Weight (kgs): _____ Blood Pressure (seated): _____

Pulse (seated): _____Resting HR (supine 5 mins): _____

Height (inches): _____

Assessments

☐ Assess Hypoglycemia Performed by: _____

☐ Medication Compliance Performed by: _____

☐ Adverse Events Monitoring Performed by: _____

Urine Pregnancy Test Completed for Women and Result:

☐ Negative ☐ Positive ☐ Not Done ☐ Not Applicable

VISIT 4 Scheduled for: _____

Comments:

Signature of Coordinator:_____ Date: _____

Visit 4 Overview

SUBJECT ID: _____ Date: _____

Weight (kgs): _____ Blood Pressure (seated): _____

Pulse (seated): _____ Resting HR (supine 5 mins): _____

Height (inches): _____

Assessments

☐ Assess Hypoglycemia Performed by: _____

☐ Medication Compliance Performed by: _____

☐ Adverse Events Monitoring Performed by: _____

Urine Pregnancy Test Completed for Women and Result:

☐ Negative ☐ Positive ☐ Not Done ☐ Not Applicable

VISIT 5 Scheduled for: _____

Comments:

Signature of Coordinator:_____ Date: _____

Visit 5 Overview

SUBJECT ID: _____ Date: _____

Weight (kgs): _____ Blood Pressure (seated): _____

Pulse (seated): _____ Resting HR (supine 5 mins): _____

Height (inches): _____

Assessments

- ☐ Medical History and Physical Examination Performed by: _____
- ☐ Laboratory Measures Performed by: _____
- ☐ HRV Performed by: _____
- ☐ CARTs Testing Performed by: _____
- ☐ Medication Compliance Performed by: _____
- ☐ Adverse Events Monitoring Performed by: _____
- ☐ Assess Hypoglycemia Performed by: _____
- ☐ EKG Performed by: _____

Urine Pregnancy Test Completed for Women and Result:

☐ Negative ☐ Positive ☐ Not Done ☐ Not Applicable

VISIT 6 Scheduled for: _____

Comments:

Signature of Coordinator: _____ Date: _____

Visit 6 Overview

SUBJECT ID: _____ Date: _____

Weight (kgs): _____ Height (inches): _____

Pulse (seated): _____ Blood Pressure (seated): _____

Resting HR (supine 5 mins): _____

Assessments

- ☐ Medical History and Physical Examination Performed by: _____
- ☐ ECG Performed by: _____
- ☐ HRV Performed by: _____
- ☐ Laboratory Measures Performed by: _____
- ☐ CARTs Testing Performed by: _____
- ☐ Assess Hypoglycemia Performed by: _____
- ☐ Medication Dispensing Performed by: _____

Urine Pregnancy Test Completed for Women and Result:

☐ Negative ☐ Positive ☐ Not Done ☐ Not Applicable

VISIT 7 Schedule for: _____

Comments:

Signature of Coordinator: _____ Date: _____

Visit 7 Overview

SUBJECT ID: _____Date: _____

Weight (kgs): _____ Blood Pressure (seated): _____

Pulse (seated): _____ Resting HR (supine 5 mins): _____

Height (inches): _____

Assessments

☐ Assess Hypoglycemia Performed by: _____

☐ Medication Compliance Performed by: _____

☐ Adverse Events Monitoring Performed by: _____

Urine Pregnancy Test Completed for Women and Result:

☐ Negative ☐ Positive ☐ Not Done ☐ Not Applicable

VISIT 8 Scheduled for: _____

Comments:

Signature of Coordinator: _____ Date: _____

Visit 8 Overview

SUBJECT ID: _____ Date: _____

Weight (kgs): _____ Blood Pressure (seated): _____

Pulse (seated): _____ Resting HR (supine 5 mins): _____

Height (inches): _____

Assessments

☐ Assess Hypoglycemia Performed by: _____

☐ Medication Compliance Performed by: _____

☐ Adverse Events Monitoring Performed by: _____

Urine Pregnancy Test Completed for Women and Result:

☐ Negative ☐ Positive ☐ Not Done ☐ Not Applicable

VISIT 9 Scheduled for: _____

Comments:

Signature of Coordinator: _____ Date: _____

Visit 9 Overview

SUBJECT ID: _____ Date: _____

Weight (kgs): _____ Blood Pressure (seated):_____

Pulse (seated): _____ Resting HR (supine 5 mins): _____

Height (inches): _____

Assessments

- ☐ Medical History and Physical Examination Performed by: _____
- ☐ Laboratory Measures Performed by: _____
- ☐ HRV Performed by: _____
- ☐ CARTs Testing Performed by: _____
- ☐ Medication Compliance Performed by: _____
- ☐ Adverse Events Monitoring Performed by: _____
- ☐ Assess Hypoglycemia Performed by: _____
- ☐ ECG Performed by: _____

Urine Pregnancy Test Completed for Women and Result:

☐ Negative ☐ Positive ☐ Not Done ☐ Not Applicable

Comments:

Signature of Coordinator: _____ Date: _____

DATE _____ VISIT: _____

SUBJECT ID _____ STAFF INITIALS _____

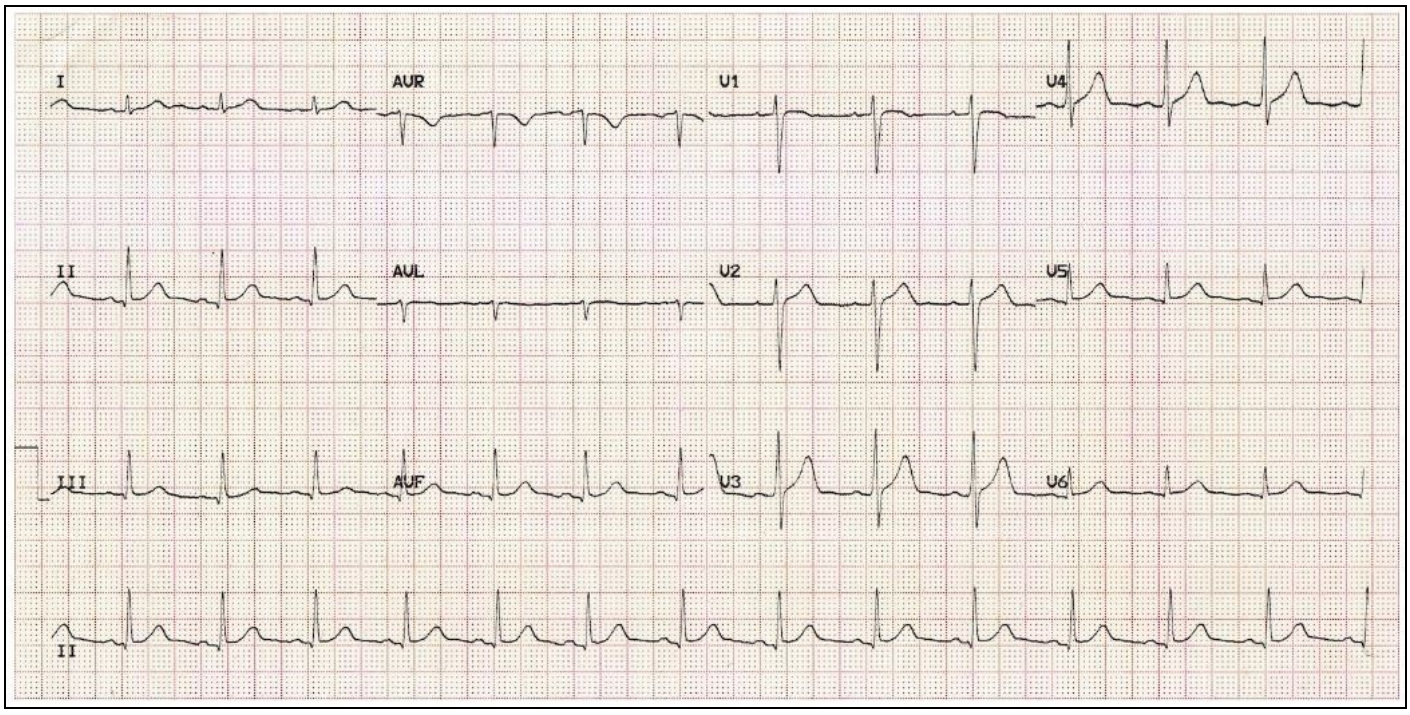
EKG Testing Cover Sheet

Interpretation:

Technician's Signature: _____ Date: _____

Physician's Signature: _____ Date: _____

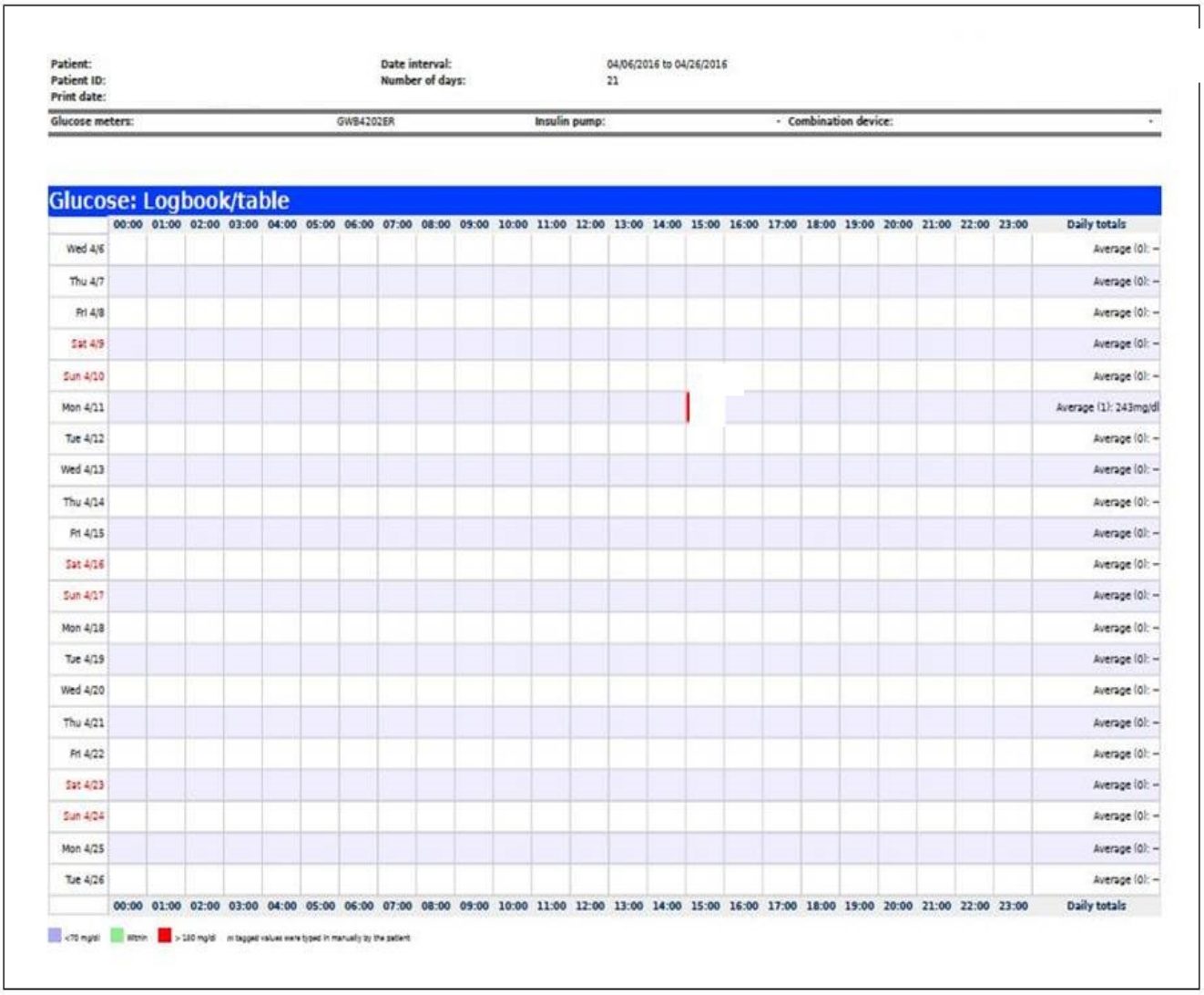
ECG Report



DATE __ __/__ __/__ __ __ __
mo day yr

SUBJECT ID __ __ __ STAFF INITIALS __ __ __

Glucometer Download Data



Patient:
Patient ID:
Print date:
Date interval: 04/06/2016 to 04/26/2016
Number of days: 21

Glucose meters: GWB4202ER Insulin pump: - Combination device: -

Glucose: Logbook/table

	00:00	01:00	02:00	03:00	04:00	05:00	06:00	07:00	08:00	09:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00	17:00	18:00	19:00	20:00	21:00	22:00	23:00	Daily totals
Wed 4/6																									Average (0): -
Thu 4/7																									Average (0): -
Fri 4/8																									Average (0): -
Sat 4/9																									Average (0): -
Sun 4/10																									Average (0): -
Mon 4/11																									Average (1): 243mg/dl
Tue 4/12																									Average (0): -
Wed 4/13																									Average (0): -
Thu 4/14																									Average (0): -
Fri 4/15																									Average (0): -
Sat 4/16																									Average (0): -
Sun 4/17																									Average (0): -
Mon 4/18																									Average (0): -
Tue 4/19																									Average (0): -
Wed 4/20																									Average (0): -
Thu 4/21																									Average (0): -
Fri 4/22																									Average (0): -
Sat 4/23																									Average (0): -
Sun 4/24																									Average (0): -
Mon 4/25																									Average (0): -
Tue 4/26																									Average (0): -
	00:00	01:00	02:00	03:00	04:00	05:00	06:00	07:00	08:00	09:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00	17:00	18:00	19:00	20:00	21:00	22:00	23:00	Daily totals

<70 mg/dl Within > 180 mg/dl m tagged values were typed in manually by the patient

Technician's Signature:_____ **Date:**_____

Physician's Signature:_____ **Date:**_____

University of Michigan Health System

University of Michigan Health Systems
Personal Diabetes Record

Study ID: _____Study ID: _____

Date	Breakfast		Lunch		Dinner		Bedtime		Pills Taken (per day)	Comments
	Blood Sugar		Blood Sugar		Blood Sugar		Blood Sugar			

Medication Dispensing

Subject ID: _____ Date of Visit: _____ Visit: _____

Was medication picked up from IDS? Yes ☐ No ☐

Date picked up: _____

Medication picked up by: _____

Prescription #: _____

Number of Tablets Dispensed: _____

Number of daily tablets prescribed by the treatment team at the conclusion of the visit today: _____

Was the patient given the study medication? ☐ Yes ☐ No

Date patient received study medication: _____

Medication given to patient by: _____

Date patient started taking the study medication: _____

Comments:_____
_____
_____
_____
_____

Form Completed by: _____ Date: _____

Medication Compliance

Subject ID: _____ Visit Date: _____ Visit: _____

How often do you skip or forget to take your study medication?

- ☐ Never/rarely
- ☐ Once in a while
- ☐ Sometimes
- ☐ Usually
- ☐ All the time

In the last week, how many doses of study medication did you skip or forget to take?

- ☐ 0
- ☐ 1-4
- ☐ 5-10
- ☐ 11-20
- ☐ 21+

Number of Tablets Dispensed at Last Visit: _____

Days Prescribed ZERO Pills Per Day: _____

Days Prescribed ONE Pill Per Day: _____

Days Prescribed TWO Pills Per Day: _____

Total Number of Tablets Expected to Be Taken: Automated

Number of Days Previous Visit Drug was in Use: Automated

Did the Patient Return Study Medication from Prior Visit? ☐ Yes ☐ No

If yes, date received by study team: _____

Number of Tablets Returned by Patient: _____

Number of Pills Taken: Automated

Percent Compliance: Automated

Since the Last Visit, was the Medication Ordered to be Stopped? ☐ Yes ☐ No

Date Study Medication was Stopped: _____

What was the Reason for Stopping the Study Medication?

☐ Intolerance/side effects

☐ Planned medical/surgical procedure

☐ Participant non-compliance with protocol

☐ Other (specify)

If other, specify:_____

Has Study Medication Been Restarted? ☐ Yes ☐ No

If yes, date study medication was restarted:_____

Stop Ordered by:_____

Since the Last Visit, was the Study Medication Ordered to be Reduced?

☐ Yes ☐ No

Date Study Medication was Reduced: _____

What was the Reason for Reducing the Study Medication?

☐ Intolerance/side effects

☐ Planned medical/surgical procedure

☐ Participant non-compliance with protocol

☐ Other (specify)

If other, specify:

_____

Has Study Medication Been Increased? ☐ Yes ☐ No

If yes, date study medication increased: _____

Change Ordered by: _____

Comments:

Medication Compliance Completed by: _____ Date: _____

DAPA-CAN Payment Form

Subject ID: _____

Visit Date: _____

Visit: _____

Amount Owed: $_____

Describe Reason for Amount: _____

Participant Payment HSIP #: _____

☐ Check that Patient Has Been Paid

Date Participant was Paid: _____

Comments:

Signature of Study Team Member: _____ Date: _____

Completion Data

Subject ID: _____

Is this a Screen Fail? ☐ Yes ☒ No

Has the Patient Completed the Study? ☐ Yes ☐ No

Date of Study Completion: ☐☐/☐☐/☐☐☐☐ ☐ N/A

Date Patient Withdrew from/Stopped the Study: ☐☐/☐☐/☐☐☐☐ ☐ N/A

Reason Patient Withdrew from/Stopped the Study: ☐ N/A

☐ Non-compliance

☐ Did not wish to continue in study

☐ Could not tolerate the supplement

☐ Hospitalization

☐ Other

If Other, Explain: _____

Date of Last Visit: ☐☐/☐☐/☐☐☐☐

Comments: _____

_____

_____

_____

_____

Completed By: _____ Date: _____