The effect of Empagliflozin versus placebo on the Rate of Arrhythmic events in Heart Failure patients

ERA-HF study

Principal Investigator:

Oren Caspi MD PhD

Department of Cardiology

Rambam Health Care Campus

2 Efron St., POB 9649, Haifa, 31096, Israel

Tel: +972-4-7772180

Fax:+972-4-7773364

Date: 14/05/2017

Version: 1.1

Document status: Final

Amendment:

PROTOCOL SIGNATURE PAGE

Protocol Title	The effect of Empagliflozin versus placebo on the Rate of Arrhythmic events in Heart Failure patients (ERA-HF study)
Protocol version and date	Final version 1.1, 14/05/2017
Study Phase	IV
Sponsor	Oren Caspi MD PhD
Sponsor representative	

By signing below, I, the investigator, approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections.

I agree to comply with the ICH-GCP, applicable Israeli MoH guidelines (2016) for the conduct of clinical trials, World Medical Association Declaration of Helsinki and applicable local regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Dr Oren Caspi.

_____

Investigator Signature Date

_____

Name Institution City Country

Table of content

List of Tables

List of abbreviations

Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AESIs	Adverse Events of Special Interest
ATP	ANTI-TACHYCARDIA PACING
BI	Boehringer Ingelheim
BNP	Brain Natriuretic Peptide
CBC	Complete Blood Count
CRF	Case Report Form
CRO	Contract Research Organization
CRTDP	Cardiac resynchronization Therapy Defibrillator
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electro Cardio Gram
eCRF	electronic Case Report File
EF	Ejection Fraction
EOS	End Of Study
GFR	Glomerular Filtration Rate
FCBP	Female of Child Bearing Potential
HbA1c	Glycated Hemoglobin A1c
ICD	Implantable Cardioverter Defibrillator
ICH-GCP	International Conference of Harmonization-Good Clinical Practice
IRB	Institutional Review Board
MDS	Myelo-Dysplastic-Syndrome
MI	Myocardial Infarction
NSVT	Non-Sustained ventricular Tachycardia
NYHA	New York Heart Association
P.O.	Per Os/ by mouth/orally
PVCs	Premature Ventricular Complexes

Q.D.	Once a Day
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of Norm
VT	Ventricular Tachycardia
WBC	White Blood Cells
WHO	World Health Organization

1 Synopsis

The effect of Empagliflozin versus placebo on the Rate of Arrhythmic events in Heart Failure patients (ERA-HF study)	
PROTOCOL NUMBER:	ERA_HF
DATE PROTOCOL FINAL:	16/03/2017
STUDY DRUG:	Empagliflozin
INDICATION :	Diabetes type 2 patients with heart failure and high arrhythmic burden
STUDY PHASE:	IV
Background and rationale:	Empagliflozin is an orally available inhibitor of the sodium-glucose co-transporter 2 (SGLT-2), that promotes enhanced glucose excretion in the urine, thereby lowering blood glucose concentrations in patients with type 2 diabetes mellitus (T2DM). The EMPA-REG OUTCOME study demonstrated a significant reduction in both heart failure hospitalization and cardiovascular death in type 2 diabetes patients with high risk for cardiovascular events. A potential mechanism underlying the pleotropic and explaining the remarkable early reduction in cardiovascular mortality may be related to the effect of empagliflozin on arrhythmic events. Multiple potential mechanisms have been suggested to mediate the positive cardiovascular effect of empagliflozin (altered cardiomyocyte metabolism, anti-arrhythmic effect, improved glycemic control, positive effect on myocardial contractility). Ventricular arrhythmias and the associated sudden cardiac death (SCD) is the leading cause of mortality in patients with heart failure. The risk for the occurrence of SCD in heart failure patients is closely related to the etiology (ischemic versus non-ischemic) and the left ventricular EF. The introduction of defibrillation therapy for primary prevention of SCD in HF patients has revolutionized the field during the last 2 decades. Nevertheless, ventricular arrhythmias remain a major cause of

	mortality for HF patients given the limited ability for risk stratification, and the dreadful prognosis associated with ventricular arrhythmias treated by defibrillation therapy. The burden of premature ventricular Complexes (PVCs) has been shown as an independent risk factor for ventricular tachyarrhythmia and SCD for healthy, ischemic and heart failure patients (with and without resynchronization and/or defibrillator therapy). Anti-arrhythmic drugs (AAD) are efficient in suppressing the occurrence of PVCs but for certain drugs, the associated with profile of adverse events and cardiotoxicity may paradoxically increase the rate of sudden cardiac death as learned by the remarkable CAST study. Be that as it may, easily suppressed PVC burden (without the associated adverse profile of AADs) has been suggested to correlate with reduction of the likelihood for SCD. Furthermore, the growing field of PVC ablation has been shown to have beneficial effect on cardiac function and the risk for ventricular arrhythmia. In summary, PVC suppression, a once neglected strategy, is now considered a promising strategy for evaluating the effect of therapeutic strategies on the risk for SCD. Empagliflozin treatment in high cardiovascular risk patients has been shown to have a relatively rapid powerful capability in reducing cardiovascular mortality. Among the suggested mechanisms mediating this effect of empagliflozin, anti-arrhythmic effect (AAE) has the highest potential to translate into a rapid clinical beneficial effect on cardiovascular mortality, while other mechanisms are known to have a lag in their clinical effect based on data from previous studies. Based on this assumption, we hypothesize that the effect of empagliflozin on the rate of cardiovascular death may be mediated by a direct effect on the risk for arrhythmic events (via a direct or an indirect effect on the myocardium). The current study aims at assessing the effect of empagliflozin on arrhythmias in diabetic patients with HF with reduced EF and relatively high arrhythmic burden.
Study Objectives	The objective of the current study is to demonstrate the effect of empagliflozin compared to placebo on the rate of ventricular arrhythmic events in type 2 diabetes patients with heart failure with reduced ejection fraction and high risk arrhythmic profile.
Primary endpoint:	The primary endpoint is the burden of premature ventricular complexes, defined as the PVCs percentage of all beats in a pre-specified period captured on ICD or CRTD/P device.

Secondary endpoints:	1. The number of non-sustained ventricular tachycardia (NSVT) episodes. 2. A composite cumulative endpoint of ventricular arrhythmia load (number of: sustained ventricular tachycardia, ventricular fibrillation, antitachycardia pacing (ATP) or delivery of shock therapy episodes. 3. The change in blood level of NT-Pro Brain Natriuretic peptide (BNP) from baseline to the end of any of the treatment periods. 4. The change in Left ventricular end diastolic diameter on echocardiography from baseline to the end of any of the treatment periods. 5. The change in left ventricular ejection fraction (EF) on echocardiography from baseline to the end of any of the treatment periods. 6. Safety endpoints (as detailed bellow).
Study Design:	The present study is a randomized, prospective, controlled, double blind, cross-over, pairwise, add on standard therapy, event driven study, comparing empagliflozin versus placebo on the ventricular arrhythmia burden in a blocked randomization stratified by ischemic versus non-ischemic cardiomyopathy and PVC burden at screening of< or ≥ to 4%. Potential study subjects will sign an informed consent prior to undergoing any study related procedure. Number of patients to be enrolled is 128. This study encompass 4 periods for each study subject: screening period of 8 weeks, first treatment period of 8 weeks, washout period of 4 weeks and a second treatment period of 8 weeks. Expected duration of subject participation is 6-7 months. Study assessments will be performed according the table of study procedures below. (Table 2) Screening period Patients will undergo screening for protocol eligibility within 56 days (8 weeks) of recruitment. Subjects meeting all the inclusion criteria and without any exclusion criteria will be enrolled after signing an informed consent. Written informed consent must be obtained before any study specific medical procedures are performed. Evaluation consists of physical examination including vital signs, laboratory-

	screening assessments including urine pregnancy test for FCBP, HbA_1c, device (ICD or CRTD/P) interrogation and echocardiography (if not done recently). <u>First treatment period</u> Randomization will take place after obtaining patient's informed consent and after fulfilling the inclusion and exclusion criteria. Patients will be assigned to empagliflozin or placebo treatment for a period of 8 weeks by a central randomization process. Evaluations consists of vital signs, blood tests, device (ICD or CRTD/P) interrogation, 24h' Holter ECG in case of ICD/CRTD/P malfunction as a backup arrhythmia assessment and echocardiography. Patient's glucose level will be monitored by a home device 3 times a day in the first week and thereafter once a week or as needed. At visit 2, an endocrinologist consultant will give to the patient instructions for antidiabetic treatment titration according to appendix 1. Patients will be treated for 8 weeks with the study drug or placebo 10 mg/day every morning. <u>Washout period</u> Study subjects will stop study drug (empagliflozin/placebo) for 4 weeks and will crossover to the second drug at the end of this period. During this period patient's glucose level will be self monitored by a home device 3 times a day in the first week and thereafter once a week or as needed. Safety laboratory examinations, HbA_1c, device interrogation and resetting, Holter ECG and echocardiography will be performed at the end of this period (visit 3). <u>Second treatment period</u> Patients will crossover to empagliflozin or placebo treatment for a period of 8 weeks. Evaluations consists of vital signs, laboratory assessments including pregnancy test for FCBP, patient's glucose level will be monitored by a home device 3 times a day in the first week and thereafter once a week or as needed. Device (ICD or CRTD/P) interrogation and 24h' Holter ECG in case of ICD/CRTD/P malfunction as a backup arrhythmia assessment and echocardiography. Patients will be treated for 8 weeks with the study drug or placebo 10 mg/day every morning.

	Medication compliance will be performed during the 2 treatment periods by counting the returned study drug blisters.
Duration of study:	The duration of the treatment period is approximately 6 months. This time span is required for completing the therapy and determining the safety profile of the drug combination and the response rate. Estimated accrual duration: 12 months. Estimated total trial duration: 18 months
Inclusion criteria: **Exclusion criteria:**	1. Heart failure patients with reduced ejection fraction (EF≤40%) assessed at least 6 months prior to recruitment and NYHA Class≥2 with ICD or CRTD/P. 2. Patients implanted with ICD, CRTD/S or CRTP device that are capable of recording PVC burden and were implanted ≥2 months prior to recruitment. 3. High risk for arrhythmic events at baseline identified by either PVC burden ≥2% **or** >≥events of non sustained VT **or** ≥1 event of sustained ventricular tachycardia **or** need for anti-tachycardia pacing **or** defibrillation therapy, during a period of 2 months prior to recruitment. 4. Diagnosis of type 2 diabetes mellitus prior to informed consent 5. HbA_1c≥7% and ≤12%. 6. Signed and dated written informed consent by date of Visit 1 in accordance with GCP legislation. 1. Evidence of ICD malfunction. 2. Antiarrhythmic treatment other than beta blockers. 3. Past exposure to SGLT2 inhibitors. 4. Uncontrolled diabetes with HbA1c>12% or glucose >240 mg/dL after an overnight fast. 5. Liver abnormalities defined by serum levels of alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase above 3 x upper limit of normal. 6. Planned cardiac procedure within 3 months. 7. Prior MI in the last 40 days. 8. Calculated eGFR< 45ml/min/1.73m2 as determined by the MDRD formula GFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)

	9. BMI>50 10. Medical History of active cancer in the past 2 years. 11. History of recurrent UTIs or genital infections 12. Systolic blood pressure <90 mmHg. 13. Alcohol or drug abuse within 3 months of informed consent. 14. Premenopausal women with planned preganancy or without adequate measures for birth-control. 15. Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial or participating in another trial involving an investigational drug and/or follow-up
Assessments **Efficacy:**	The following evaluations will be conducted to judge the efficacy of the treatment regimen: Primary efficacy assessment is PVCs burden. PVCs burden will be evaluated as a part of the device interrogation on visit 1 to assess device integrity and proper function, in visit 2 to assess patient's eligibility for the study according to in- and exclusion criteria. In visit 3 and 5 to assess for treatment efficacy. Assessment of the PVCs will be based on PVC counters for the various ICD/CRTD/P interrogated. Monitor counter reset will be conducted on visit 1,2,3,4 and 5. In the case of device malfunction, counter malfunction or any other cause of inability to readout the device PVC counter measurement, PVC burden will be calculated from a 12 Lead ECG Holter for 24 hours conducted at one of the last 7 days of the period assessed **Secondary efficacy assessments are:** **NSVT rate:** Non-sustained ventricular tachycardia rate is defined as the the number of NSVT events in a pre-specified period captured on ICD or CRTD/P device interrogation or as a backup information (in case of ICD or CRTD/P malfunction) on Holter ECG. The device will be activated along the whole study period and data will be captured on the CRF at visits 1 to 5. **Composite endpoint of: sustained VT+VF, ATP or delivery of shock therapy**: All the four parameters will be captured on ICD or CRTD/P device interrogation. Data from study device will be captured on the CRF at visits 1 to 5.

Safety:	**NT-Pro-BNP**: NT-Pro-BNP Is a plasma level pf B-type Natriuretic Peptide used as a blood test for diagnosing and evaluation the presence/severity of heart failure. Plasma level will be performed at visits:2 to 5. **Left ventricular end diastolic diameter**: Left ventricular end diastolic diameter is defined as the cross-sectional diameter of the left ventricle, including the septum and the posterior thicknesses in diastole. The assessment is performed by echocardiography done at visits: 1 to 3 and 5. Ejection fraction: Ejection fraction is defined as the ratio of the stroke volume to the end-diastolic volume in the left ventricle as performed by echocardiography and expressed by percentage. The assessment is performed by echocardiography done at visits: 1 to 3 and 5. The following evaluations will be conducted to assess the safety of the treatment regimens: Adverse events Clinical laboratory evaluations (hematology, biochemistry, urine analysis) Complete physical examination including vital signs. Concomitant medication and procedures
Sample size consideration	The planned sample size is 128 subjects, 64 in each study arm. When the sample size in each sequence group is 64, (a total sample size of 128) a 2 x 2 crossover design will have 80% power to detect a difference in Mean reduction of -10.0, assuming that the Crossover ANOVA MSE is 28.284 (the Standard deviation of differences, sd, is 40.0) using a two group T-test (Crossover ANOVA) with a 0.05 two-sided significance level.
Efficacy analysis:	The primary efficacy is the percentage of PVCs during the 2 months of empagliflozin treatment compared with the percentage of PVC on placebo. The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the carry-over effect in the primary endpoint between the two sequences. If no carry-over effect will be observed, then The Paired T-test or non-parametric Signed-rank test for two means (as is appropriate) will be applied for analyzing the difference in the above changes between the tested treatment and placebo.

	Otherwise, if a carry-over effect will be found statistically significant, then the MMRM model (Mixed-effect model for repeated measures) will be applied for analyzing the difference in the above reduction between the tested treatment and the placebo.
Safety analysis:	Data from all subjects who receive any study drug will be included in the safety analyses. The severity of the toxicities will be graded according to the NCI CTC whenever possible. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events will be summarized by the worst NCI CTC grade. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTC Grade 3 or Grade 4, study-drug-related events, and serious adverse events will be summarized separately. Laboratory data will be graded according to NCI CTC severity grade.

2 Background Information

2.1 Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the deviation will be reported to the IRB according to its policies and procedures.

2.2 Background

Empagliflozin is an orally available inhibitor of the sodium-glucose co-transporter 2 (SGLT-2), that promotes enhanced glucose excretion in the urine, thereby lowering blood glucose concentrations in patients with type 2 diabetes mellitus (T2DM). The EMPA-REG OUTCOME study[1] demonstrated a significant reduction in both heart failure hospitalization and cardiovascular death in type 2 diabetes patients with high risk for cardiovascular events. A potential mechanism underlying the pleotropic and explaining the remarkable early reduction in cardiovascular mortality may be related to the effect of empagliflozin on arrhythmic events.

T2DM is among the most common chronic diseases with increasing prevalence and incidence [2]. T2DM is associated with profound cardiovascular disease (CVD) burden which is considered as a primary contributor to T2DM mortality in the setting of diabetes in the form of coronary artery disease (CAD), cerebrovascular disease, peripheral vascular disease (PVD), and heart failure (HF). T2DM is associated with 2-5-fold risk for heart failure with reduced or preserved left ventricular ejection fraction(EF). The key mechanisms contributing to this include: (1) Increased risk for CAD and a dreadful prognosis associated with the T2DM-CAD duet; (2) Associated atherosclerosis and reduced vascular compliance leading to hypertension, afterload augmentation and impaired cardiac efficiency; (3) Abnormal metabolic response to adverse

stressors (i.e. ischemia) resulting in abnormal metabolism, lipotoxicity, cardiac steatosis, production of advanced glycation end products affecting diastolic function, and reduction of cardiac efficiency, all collectively known as “diabetic cardiomyopathy”.

The recent introduction of renal sodium-glucose cotransporter 2 (SGLT2) inhibitors target a novel mechanism that affect glucose plasma levels. Briefly, SGLT2 receptors are responsible for absorbing glucose during normoglycemia and provide a buffering mechanism during hyperglycemia (allowing glucose urinary excretion) resulting in glycosuria. Importantly, In T2DM patients there is a paradoxical increase in SGLT2 expression and in the its thresholds for glucose urinary excretion. Empagliflozin, a member of the, recently introduced, clinically available, SGLT2 inhibitors was shown to effectively lower plasma glucose levels with a mean hemoglobin A1C (HbA_1c) reduction of -0.7%[3, 4] in both phase 2 and 3 clinical trials[1, 5, 6]. The EMPA-REG OUTCOME study, evaluated the cardiovascular effects of empagliflozin therapy in patients with high cardiovascular risk (Established significant coronary artery disease, recent unstable angina or myocardial infarction, recent stroke or peripheral artery disease). The study demonstrated a reduction in the primary composite outcome (that included death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). Importantly, while the study did not show a significant effect of empagliflozin on the rate of myocardial infarction or stroke, empagliflozin therapy resulted in remarkable and significant reduction in cardiovascular mortality (38% relative risk reduction). Surprisingly, the effect of empagliflozin on the occurrence of cardiovascular events appeared very early within the course of the study (separation of curves started as early as less than 1 month from treatment initiation). Multiple potential mechanisms have been suggested to mediate the positive cardiovascular effect of empagliflozin (altered cardiomyocyte metabolism, anti-arrhythmic effect, improved glycemic control, positive effect on myocardial contractility)[3].

Ventricular arrhythmias and the associated sudden cardiac death (SCD) is the leading cause of mortality in patients with heart failure. The risk for the occurrence of SCD in heart failure patients is closely related to the etiology

(ischemic versus non-ischemic) and the left ventricular EF [7]. The introduction of defibrillation therapy for primary prevention of SCD in HF patients has revolutionized the field during the last 2 decades. Nevertheless, ventricular arrhythmias still remain a major cause of mortality for HF patients given the limited ability for risk stratification, and the dreadful prognosis associated with ventricular arrhythmias treated by defibrillation therapy[8, 9]. The burden of premature ventricular Complexes (PVCs) has been shown as an independent risk factor for ventricular tachyarrhythmia and SCD for healthy, ischemic and heart failure patients (with and without resynchronization and/or defibrillator therapy).[10-19] Anti-arrhythmic drugs (AAD) are efficient in suppressing the occurrence of PVCs but for certain drugs, the associated with profile of adverse events and cardiotoxicity may paradoxically increase the rate of sudden cardiac death as learned by the remarkable CAST study.[20] Be that as it may, easily suppressed PVC burden (without the associated adverse profile of AADs) has been suggested to correlate with reduction of the likelihood for SCD[21]. Furthermore, the growing field of PVC ablation has been shown to have beneficial effect on cardiac function and the risk for ventricular arrhythmia[22]. In summary, PVC suppression, a once neglected strategy, is now considered a promising strategy for evaluating the effect of therapeutic strategies on the risk for SCD[23].

Empagliflozin treatment in high cardiovascular risk patients with diabetes has been shown to have a relatively rapid powerful capability in reducing cardiovascular mortality. Among the suggested mechanisms mediating this effect of empagliflozin, anti-arrhythmic effect (AAE) has the highest potential to translate into a rapid clinical beneficial effect on cardiovascular mortality, while other mechanisms are known to have a lag in their clinical effect based on data from previous studies. Based on this assumption, we hypothesize that the effect of empagliflozin on the rate of cardiovascular death may be mediated by a direct effect on the risk for arrhythmic events (via a direct or an indirect effect on the myocardium). The current study aims at assessing the effect of empagliflozin on arrhythmias in diabetes patients with HF with reduced EF and relatively high arrhythmic burden.

2.3 Investigational product

Empagliflozin (Jardiance®) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2).

The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4- [[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S).
Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91.
Mechanism of action: Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

2.4 Preclinical data

Studies in rodents and non rodents animals evaluated carcinogenesis, mutagenesis and impairment of fertility.

No increase in carcinogenesis (Renal tubule adenomas and carcinomas were observed in male mice at 1000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg.)

Mutagenesis was not observed in in vitro mutagenicity assays.

Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

2.5 Clinical data to date

Adverse reactions excluding hypoglycemia reported in ≥2% of patients treated with empagliflozin and greater than placebo in pooled placebo-controlled

clinical studies of empagliflozin monotherapy or combination therapy reflecting exposure of 1976 patients to empagliflozin:

Table 1

	Number (%) of patients		
	Placebo N=995	Empagliflozin 10 mg N=999	Empagliflozin 25 mg N=977
Urinary tract infection	7.6%	9.3%	7.6%
Female genital mycosis	1.5%	5.4%	6.4%
Upper respiratory tract infection	3.8%	3.1%	4.0%
Increased urination	1.0%	3.4%	3.2%
Dyslipidemia	3.4%	3.9%	2.9%
Arthralgia	2.2%	2.4%	2.3%
Male genital mycotic infections	0.4%	3.1%	1.6%
nausea	1.4%	2.3%	1.1%

Other adverse events observed in clinical studies: thirst was reported in 1.5% to 1.7% of patients treated by empagliflozin, most probably secondary to volume depletion due to osmotic diuresis properties of empagliflozin. Volume depletion caused by osmotic diuresis is the cause of: arterial hypotension, dehydration and orthostatic hypotension that were reported in 0.3% to 0.5% in clinical trials with empagliflozin.

Mild impairment in renal function (increased serum creatinine or decrease in GFR) especially in persons with preexisting moderate renal impairment was noticed in clinical trials involving empagliflozin.

Dose related increase in LDL cholesterol was observed in 4.6% to 6.5% versus 2.3% in the placebo group.

Hypoglycemia was observed in clinical trials when empagliflozin (10mg) was administrated as monotherapy in 0.4% of patients. Combination therapy with metformin resulted in hypoglycemia rate of 1.8% (versus 0.5% with placebo and metformin). Combination therapy with insulin resulted in hypoglycemia rate of

19.5% (versus 20.6% with placebo and insulin). Combination theraphy with metformin and sulfonylura resulted in hypoglycemia rate of 16.1% (versus 8.4% with placebo and the baseline drugs).

2.6 Known and potential risks and benefits

Hypotension

Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating empagliflozin, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected

Impairment in Renal Function

Empagliflozin increases serum creatinine and decreases eGFR. The risk of impaired renal function with Empagliflozin is increased in elderly patients and patients with moderate renal impairment. More frequent monitoring of renal function is recommended in these patients renal function should be evaluated prior to initiating empagliflozin and periodically thereafter.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin.

Genital Mycotic Infections

Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Risk for female genital infection is 5.4%

(versus 1.5% with placebo). Management includes monitoring and treatment as appropriate.

Urinary Tract Infections

Empagliflozin (10mg) increases the risk for urinary tract infections (UTI) including pyelonephtritis and sepsis due to urinary tract infections. The risk for UTI increases with age and with female sex. Risk for UTI is 9.3% (versus 7.6% with placebo). Management includes monitoring and treatment as appropriate.

Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increase in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with empagliflozin or any other antidiabetic drug.

3 Trial Objectives and Purpose

We hypothesize that the effect of empagliflozin on the rate of cardiovascular death may be mediated by a direct effect on the risk for arrhythmic events (via a direct or an indirect effect on the myocardium). The current study aims at assessing the effect of empagliflozin on arrhythmias in diabetic patients with heart failure with reduced EF and relatively high arrhythmic burden.

3.1 Primary Objective

The objective of the current study is to demonstrate the effect of empagliflozin compared to placebo on the rate of ventricular arrhythmic events in type 2 diabetes patients with heart failure with reduced ejection fraction and high risk arrhythmic profile.

3.2 Secondary Objectives

To evaluate the effect of Empagliflozin on cardiac function,using molecular (NT-Pro_BNPlevels0, echocardiographic and physiological markers of myocardial function.

4 Trial Design

4.1 Primary and secondary endpoints

4.1.1 Primary Endpoint

The primary endpoint is the burden of premature ventricular complexes, defined as the PVCs percentage of all beats in a pre-specified period captured on ICD or CRTD/P device.

PVC burden will be calculated according to device interrogation. In case of device failure to appropriately monitor the PVC burden, 24hr 12 lead holter ECG recording will be used as a complimentary method for arrhythmia assessment.

4.1.2 Secondary Endpoints

1. The number of non-sustained ventricular tachycardia (NSVT) episoedes, defined as the NSVT number in a pre-specified period captured on ICD or CRTD/P device.
2. A composite cumulative endpoint of ventricular arrhythmia load (number of: sustained ventricular tachycardia, ventricular fibrillation, antitachycardia pacing (ATP) or delivery of shock therapy episodes, defined as the arrhythmias number in a pre-specified period captured on ICD or CRTD/P device.
3. The change in blood level of NT-Pro Brain Natriuretic peptide (BNP) from baseline to the end of any of the treatment periods
4. The change in Left ventricular end diastolic diameter on echocardiography from baseline to the end of any of the treatment periods.
5. The change in Left ventricular ejection fraction (EF) on echocardiography from baseline to the end of any of the treatment periods.
6. Safety.

4.2 Overall study design

The present study is a randomized, prospective, controlled, double blind, cross-over, pairwise, add on standard therapy, event driven study, comparing empagliflozin versus placebo on the ventricular arrhythmia burden in a blocked randomization stratified by ischemic versus non-ischemic cardiomyopathy and PVC burden at screening of< or ≥ to 4%.

Patients will be recruited from the congestive heart failure clinic of the study site and treated for up to 8 weeks with the study drug (or placebo) and then another 8 weeks with placebo (or study drug) with a washout period of 4 weeks between the two treatment periods. Potential study subjects will sign an informed consent prior to undergoing any study related procedure. Generally, study medications should be continued until intolerance. Treatment after completion of the study is at the discretion of the investigator.

Up to 128 patients are planned to be enrolled. Enrollment time of the study is one year.

This study encompass 4 periods for each study subject: screening period of 8 weeks, first treatment period of 8 weeks, washout period of 4 weeks and a second treatment period of 8 weeks. Expected duration of subject participation is 6-7 months.

Study assessments will be performed according the table of study procedures below. (Table 2)

Screening / run in period

Patients will undergo screening for protocol eligibility within 56 days (8 weeks) of recruitment.

Subjects meeting all the inclusion criteria and do not meet any exclusion criteria will be enrolled after signing an informed consent.

Written informed consent must be obtained before any study specific medical procedures are performed. Evaluation consists of physical examination

including vital signs, laboratory-screening assessments including urine pregnancy test for FCBP, HbA_1c, device (ICD or CRTD/P) interrogation and echocardiography (if not done recently).

First treatment period

Randomization will take place after obtaining patient's informed consent and after fulfilling the inclusion and exclusion criteria. Patients will be assigned to empagliflozin or placebo treatment for a period of 8 weeks by a central randomization process.

Evaluations consists of vital signs, laboratory assessments blood examination, device (ICD or CRTD/P) interrogation, 24h' Holter ECG in case of ICD/CRTD/P malfunction as a backup arrhythmia assessment and echocardiography. Patient's glucose level will be monitored by a home device 3 times a day in the first week and thereafter once a week or as needed. At visit 2, an endocrinologist consultant will give to the patient instructions for antidiabetic treatment titration according to appendix 1.

Patients will be treated for up to 8 weeks with the study drug or placebo 10 mg/day every morning.

Washout period

Study subjects will stop study drug (empagliflozin/placebo) of the first treatment period and will be given placebo for a washout period of 4 weeks and will crossover to the second drug at the end of this period at the beginning of the next treatment period. During this period, patient's glucose level will be monitored by a home device 3 times a day in the first week and thereafter once a week or as needed. Safety laboratory examinations, HbA_1c, device interrogation and resetting, Holter ECG and echocardiography will be performed at the end of this period (visit 3). In the case of abnormal glucose levels during the washout period, diabetes treatment will be changed according to appendix 1 aiming to maintain glucose levels at normal range.

Second treatment period

Patients will crossover to empagliflozin or placebo treatment for a period of 8 weeks.

Evaluations consists of vital signs, laboratory assessments including pregnancy test for FCBP. Patient's glucose level will be monitored by a home device 3 times a day in the first week and thereafter once a week or as needed. Device (ICD or CRTD/P) interrogation and 24h' Holter ECG in case of ICD/CRTD/P malfunction as a backup arrhythmia assessment and echocardiography. In the case of abnormal glucose levels during the second treatment period, diabetes treatment will be changed according to appendix 1 aiming to maintain glucose levels at normal range.

Patients will be treated for up to 8 weeks with the study drug or placebo 10 mg/day every morning.

Medication compliance will be performed during the two treatment periods by counting the returned study drug blisters.

Accompanying scientific program

In order to gain a deeper insight into the mechanism of action of empagliflozin in individuals with diabetes with heart failure and arrhythmogenic risk, additional research projects will be performed based on urine and blood samples of patients participating in this trial.

Additional samples will be drawn at different time points (visits 2-5) for the scientific projects, Furthermore, patients will be asked to agree, that the leftovers of the samples accompanying scientific program may be stored and used for other scientific analyses and projects. The following urine and blood examinations will be performed at the treatment periods: urine and blood biobank samples (This will require a separate IRB approval.), electrolytes urine examination, 24h urine collection, 6 minute walk distance and cardiopulmonary exercise test.

4.2.1 Visit schedule and assessments

Table 2 visit schedule and assessments

Trial Period	Screening	Treatment Period			
Visit	**1**	**2**	**3**	**4**	**5**
Study Week	**0**	**8**	**16**	**20**	**28**
Days from randomization	**-56**	**0**	**56**	**84**	**140**
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Medical History	X				
Concomitant therapy	X	X	X	X	X
Demographics	X				
Physical Exam	X	X			
Vital Signs	X	X	X	X	X
Height	X				
Weight	X	X	X	X	X
Randomization		X			
Pregnancy test[1]	X	X		X	X
Home Blood glucose monitoring[2]		X	X	X	X
Safety blood samples[3]	X	X	X		X
HbA_1c	X		X		X
Device Interrogation	X	X	X	X	X
Monitor Counter Reset	X	X	X	X	X
12 Lead Holter ECG for 24hrs		X	X		X
Echocardiography	X[4]	X	X		X
NT-Pro-BNP		X	X	X	X
Medication Compliance check			X		X

[1] For female patients with childbearing potential (Urine pregnancy test).

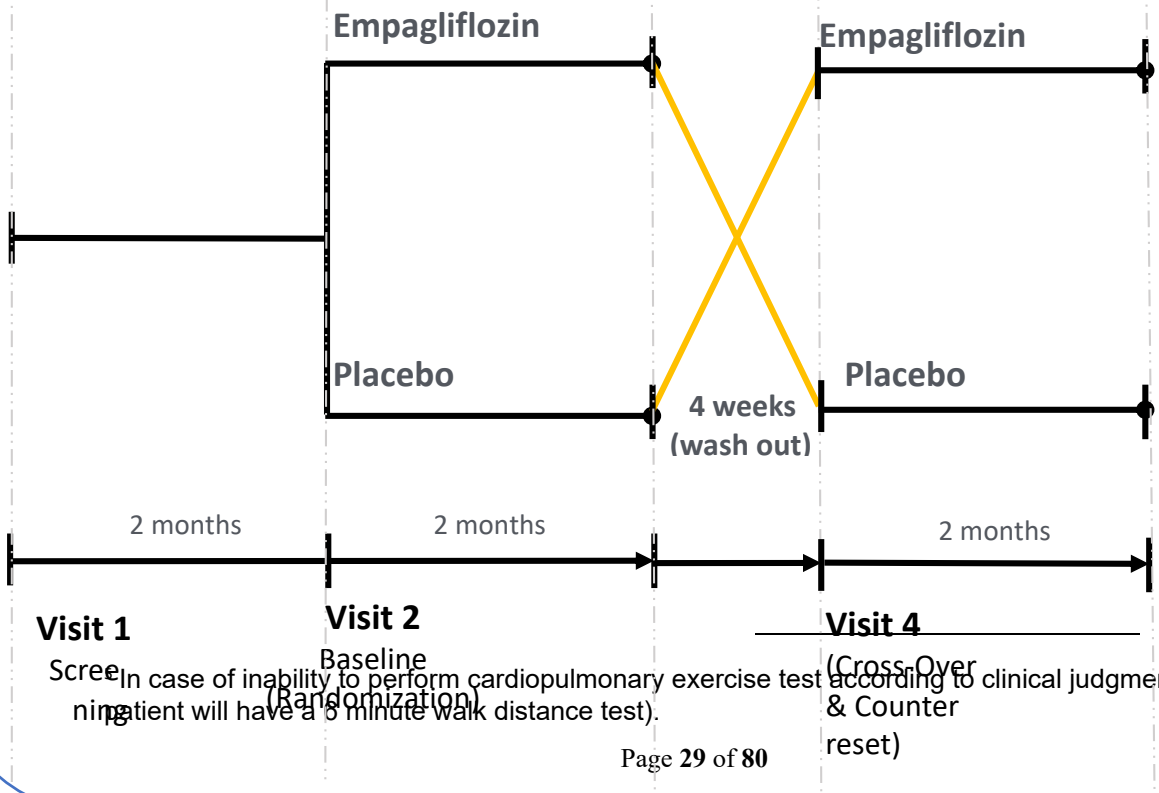
[2] Patients without means for daily home blood glucose monitoring will be given a device on visit 2. Glucose level will be measured 3 times a day in the first week and thereafter once a week or as needed. Additional measurements are warranted in the case of hypo- or hyperglycemia signs or symptoms.

[3] Safety blood samples include: Fasting blood samples (8hr fasting), Liver and kidney functions, urine dipstick for signs of infection and ketoacidosis (if positive leukocyte esterase (WBC) or nitrites a midstream urine sample for urine culture will be taken.

[4] Echocardiography will be done if needed to verify patient suitability for inclusion criteria.

Trial Period	Screening	Treatment Period			
Visit	1	2	3	4	5
Study Week	0	8	16	20	28
Days from randomization	-56	0	56	84	140
Endocrinologist consult		X			
Biobank samples		X	X	X	X
Urine Analysis (Electrolytes)		X	X	X	X
24hr Urine Sample collection		X	X	X	X
CardioPulmonary Exercise Test & 6 minute walk distance[5]		X	X		X
Adverse events		X	X	X	X

Study scheme



In case of inability to perform cardiopulmonary exercise test according to clinical judgment , patient will have a 6 minute walk distance test).

	Visit 3 Analysis 1	Visit 5 Analysis 2

4.2.2 Visit Procedures

Screening visit (day -56 to 0)

1. Obtain patient signed informed consent.

   Prior to a subject's participation in the trial, an Informed Consent form will be signed and personally dated by the subject and by the person who conducted the Informed Consent discussion.

   If a subject is unable to read, an impartial witness should be present during the entire Informed Consent discussion. After the written Informed Consent, form is read and explained to the subject and after the subject has orally consented to participating in the trial if the subject is capable of doing so she/he should sign and personally date the Informed Consent form, the witness should sign and personally date the consent form. By signing the consent form if the subject is unable to sign, then the witness attests that the information in the consent form was accurately explained to, and apparently understood by the subject and that Informed Consent was freely given by the subject.

   Prior to participation in the trial, the subject will receive a copy of the signed and dated written Informed Consent form. During participation in the trial, the subject will receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

   The investigator should document in the source data that the Informed Consent was signed prior to subject's participation in the study and according to the ICH guidelines, as described above.

2. Review patient's eligibility for the study according to in- and exclusion criteria.
3. Demographic data will be recorded (sex, age, ethnic origin)
4. Review and record relevant medical history. Participant's medical history should be fully documented at screening, to ensure compliance with study inclusion criteria and the absence of circumstances mentioned in the exclusion criteria. Medical history information must include, but not be limited to, past and present major illnesses, any previous surgery/operations and any current ongoing illness.
5. Review and record current medical condition history (T2DM control, NYHA status, Heart failure therapy).
6. Perform a complete physical examination. The treating investigator will conduct a complete physical examination and assess subject's performance

status at screening in order to ensure compliance with study inclusion criteria and the absence of circumstance mentioned in the exclusion criteria.

7. Measure vital signs at screening in order to ensure compliance with study criteria. Vital signs measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Body weight and height will also be measured. Measurements that may potentially constitute future adverse events (e.g. hypoglycemia, hypotension etc.) should be graded in the medical history form at baseline according to CTC as described in 8.1.3 below.
8. Collect safety blood and urine samples. Including hematology and chemistry blood examinations and urine dipstick for signs of ketoacidosis or infection.

   Hematology: Testing of Complete Blood Counts (CBC) including differential and platelet count will be performed at screening, in order to ensure compliance with study inclusion criteria (5 ml blood per sample). Every out-of-range value will be assessed by a physician and deemed as either clinically significant (S) or not significant (NS).

   Chemistry: Serum chemistry panel will consist of sodium, potassium, calcium, protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and fasting glucose. Chemistry will be performed at screening, in order to ensure compliance with study inclusion criteria (5-10 ml blood per sample). Every out-of-range value will be assessed by a physician and deemed as either clinically significant (S) or not significant (NS).

11. Review menopausal status and in women of childbearing potential a urine pregnancy test (β-HCG) will be performed.
12. Collect venous blood will be drawn for HbA_1c.
13. Perform device interrogation by an electrophysiological technician for verification of arrhythmogenic risk according the eligibility criteria.
14. Perform monitor counter reset by an electrophysiological technician.
15. Perform echocardiography for verification of EF≤40% according to the eligibility criteria (if not done in the last 6 months).
16. Review concomitant medications. All prior treatments (medications) received by the subject within 30 days of the initial screening visit and during the study will be recorded on the subject's CRF including the name of the treatment, indication, total daily dose, frequency and the start and stop dates. Any medications (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study will be documented.

Collection of information on standard of care treatment will be done as part of medications records during the study.

17. Invite study subject to study site for Holter ECG installation in one of the 7 days before the next visit.

Base line visit (2) (day 0 ±7 days)

1. Patient's enrollment. Eligibility for the study according to inclusion and exclusion criteria will be rechecked but lab tests not repeated) if all criteria are fulfilled and there is no significant change in the subject's health, he/she will be enrolled into the study to receive the first study drug.
2. Get patient randomization number.
3. Begin study drug treatment (active or placebo), provide patient 60 tablets and give treatment instructions for home use.
4. Perform a complete physical examination.
5. Measure vital signs in order to ensure compliance with study criteria. Vital signs measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Body weight will also be measured. Measurements that may potentially constitute future adverse events (e.g. hypertension, fever etc.) should be graded in the medical history form at baseline according to CTC as described in 8.1.3 below
6. Collect safety blood and urine samples. Including hematology and chemistry blood examinations and urine dipstick for signs of ketoacidosis or infection.
7. Review menopausal status and in women of childbearing potential perform a urine pregnancy test (β-HCG).
8. Collect home diary glucose results and provide a new diary for the following period.
9. Provide home diary for daily blood glucose determination.
10. Perform device interrogation.
11. Perform Monitor counter reset.
12. Collect Holter ECG device results and invite study subject to study site for Holter ECG installation in one of the 7 days days before the next visit.
13. Perform echocardiography for determination of EF
14. Consult endocrinologist for glucose lowering medication titration
15. Collect blood examination for NT-Pro-BNP
16. Collect urine and blood examination for biobank sample
17. Collect urine for electrolyte concentration

18. Obtain 24 hours urine sample collection
19. Perform cardiopulmonary exercise test (In case of inability to perform cardiopulmonary exercise test according to clinical judgment, patient will have a 6 minute walk distance test)
20. Perform 6 minute walk distance
21. Review concomitant medications.
22. Document adverse events.

Treatment washout visit (3) (day 56 ±7 days)

1. Provide patient with 30 tablets of study drug for home use
2. Collect study drug blisters returned by patient.
3. Measure vital signs in order to ensure compliance with study criteria. Vital signs measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Body weight will also be measured.
4. Collect safety blood and urine samples. Including hematology and chemistry blood examinations and urine dipstick for signs of ketoacidosis or infection.
5. Remind patient to follow the endocrinologist intructions given on visit 2.
6. Collect venous blood that will be drawn for HbA1c.
7. Collect home diary glucose results and provide a new diary for the following period.
8. Perform device interrogation.
9. Perform Monitor counter reset.
10. Collect Holter ECG device results and invite study subject to study site for Holter ECG installation in one of the 7 days days before the next visit.
11. Perform echocardiography for determination of EF
12. Collect blood examination for NT-Pro-BNP
13. Collect urine and blood examination for biobank sample
14. Collect urine for electrolyte concentration
15. Obtain 24 hours urine sample collection
16. Perform cardiopulmonary exercise test (In case of inability to perform cardiopulmonary exercise test according to clinical judgment , patient will have a 6 minute walk distance test)

17. Perform 6 minute walk distance
18. Review concomitant medications.
19. Document adverse events.

Treatment visit (4) (day 84 ±7 days)

1. Provide patient with 60 tablets of study drug for home use
2. Collect study drug blisters returned by patient.
3. Measure vital signs in order to ensure compliance with study criteria. Vital signs measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Body weight will also be measured.
4. Review menopausal status and in women of childbearing potential perform a urine pregnancy test (β-HCG).
5. Remind patient to follow the endocrinologist intructions given on visit 2.
6. Collect home diary glucose results and provide a new diary for the following period.
7. Perform device interrogation.
8. Perform Monitor counter reset.
9. Collect blood examination for NT-Pro-BNP
10. Collect urine and blood examination for biobank sample
11. Collect urine for electrolyte concentration
12. Obtain 24 hours urine sample collection
13. Review concomitant medications
14. Document adverse events.

End of Study visit (5) (day 140 ±7 days)

1.
2. Collect study drug blisters returned by patient.
3. Measure vital signs in order to ensure compliance with study criteria. Vital signs measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Body weight will also be measured.
4. Collect safety blood and urine samples. Including hematology and chemistry blood examinations and urine dipstick for signs of ketoacidosis or infection.
5. Review menopausal status and in women of childbearing potential perform a urine pregnancy test (β-HCG).
6. Collect venous blood that will be drawn for HbA1c.

7. Collect home diary glucose results.
8. Perform device interrogation.
9. Perform Monitor counter reset.
10. Collect Holter ECG device results.
11. Perform echocardiography for determination of EF
12. Collect blood examination for NT-Pro-BNP
13. Collect urine and blood examination for biobank sample
14. Collect urine for electrolyte concentration
15. Obtain 24 hours urine sample collection
16. Perform cardiopulmonary exercise test (In case of inability to perform cardiopulmonary exercise test according to clinical judgment , patient will have a 6 minute walk distance test)
17. Perform 6 minute walk distance.
18. Review concomitant medications.
19. Document adverse events.

4.3 Trial treatment

4.3.1 Investigational therapy

Empagliflozin and placebo is supplied to the study investigators by the Boehringer Ingelheim Company via the sponsor. Empagliflozin is supplied as 10 mg tablets packaged in blister packs.

Labels will comply with the legal requirements of Israel and be printed in Hebrew, Arabic and English. The storage conditions for study drug will be described on the medication label. Patients will receive study drug 10mg by the oral route q.d. if in the opinion of the investigator the patient is benefiting from treatment with this study drug, and in the absence of any safety concerns. Treatment will be withheld only in the case of limiting toxicities.

4.3.2 Treatment assignment

Treatment assignment will take place only after getting patients' Informed consent and determining patient's eligibility. Each patient will be assigned a unique patient number. Once assigned, numbers for any non-evaluable or discontinued patient will not be reused.

A central randomization based on a 1:1 basis, of a pre-determined randomization schedule prepared by the data management of the CRO will provide the investigator treatment allocation to empagliflozin or placebo by fax or email. Treatment allocation and a unique randomization number will be sent by the CRO to the investigator soon after a copy of the inclusion and exclusion criteria will be fulfilled and signed by the investigator in the appropriate CRF form and sent by fax or email to the data management of the study CRO. Email address: rmarilus@netvision.net.il. Fax number: 972-9-9540-457.

Blinding

The investigators, the Sponsor, and any personnel involved in patients' assessment, monitoring and data management will be blinded to the patient assignment.

The active study drug and placebo will be packaged and labeled by Boehringer Ingelheim Company.

All study drugs blisters and tablets will appear identical to ensure blinding.

Study drugs will be dispensed by the site pharmacy, in accordance with the randomization code system and the blinded study team will have no access to study drug or placebo, or randomization information.

Emergency Identification of Study drug

In case of a medical emergency, when the study drug assignment is needed to make treatment decisions for the patient, the investigator may unblind the patient's drug assignment. The Sponsor and medical monitor should be notified of the event prior to breaking of the code, if possible. If this is not possible, the Sponsor should be notified immediately afterwards, and the patient's drug code assignment should not be revealed. The circumstances leading to the breaking of the code should be fully documented, in the investigator's study files and in the patient's source documentation. Treatment assignment should not be recorded in any study documents.

The reason for breaking the blind must be documented in the patient's CRF and in the patient's medical records.

Documentation of contact or attempted contact with the clinical research physician prior to breaking the blind must also be documented in the patient's medical records.

4.4 Study drug interruption or discontinuation

4.4.1 Discontinuation of study drug

The following events will be considered as reasons for drug discontinuation:

- Subject's request
- Intolerable grade 3/4 adverse drug reaction that is judged by the investigator to be either physically or psychologically detrimental to the patient.
- Any study drug interruption that exceeds 14 consecutive days.
- Patient's non-compliance with study procedures as evaluated by PI and/or sponsor as warranting therapy discontinuation.
- Other reasons regarded by the PI as warranting therapy discontinuation.
- Premature study termination as described below.
- Pregnancy. If a woman becomes pregnant during the treatment period of the study, she will immediately be withdrawn from the study and will be followed up until delivery.

The investigator should contact the subject either by telephone or through a personal visit or a responsible relative must be contacted to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing. If the reason for removal of a patient from the study treatment is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the case report form.

The section for "Study Completion" in the CRF must be completed for all patients. The reason for early discontinuation should be given, even if the patient refused to return for a final visit. Patients whose treatment is

discontinued prematurely due to significant adverse events (AEs) should continue to be followed until resolution of the AE, and the relevant sections of the CRF should be completed as appropriate. Patients who are discontinued due to clinically significant abnormalities in clinical laboratory results should continue to be evaluated until the abnormality resolves or is judged permanent.

Patients lost to follow up should be recorded as such on the CRF. If patients refuse to return for these visits or are unable to do so, the patient should be considered off-study.

Subjects withdrawn from the study will not be replaced.

4.4.2 Study drug interruption

No study drug interruption is allowed unless for safety reasons.

4.5 Study Discontinuation

The patient or the investigator can decide to discontinue subject participation on study.

Possible reasons of premature study termination include:

- Death
- Participation in another investigational drug trial
- Loss to follow-up
- Patient withdrawal of consent
- Malfunction of CRTD/ICD.
- Clinical need to begin antiarrhythmic drug excluding beta blockers.
- Occurance of myocardial infarction.
- Sepsis as a consequence of UTI or genital infection.
- Administrative problems (of the whole study)
- Patient of investigator not compliant with study protocol.

- Occurrence of an AE which makes discontinuation desirable or necessary in the investigators' and/or the patients' opinion

In those cases, no patient follow-up will be recorded.

The section for "Study Completion" in the CRF must be completed for all patients. The reason for early discontinuation should be given, even if the patient refused to return for a final visit. Patients who discontinue prematurely due to significant adverse events (AEs) should continue to be followed until resolution of the AE, and the relevant sections of the CRF should be completed as appropriate. Patients who are discontinued due to clinically significant abnormalities in clinical laboratory results should continue to be evaluated until the abnormality resolves or is judged permanent.

4.6 Premature whole study termination

- Administrative problems e.g.: recurrent serious or severe ADR clinically evaluated by PI and/or sponsor as warranting whole study termination.
- A decision made by the sponsor and/or IRB/EC and/or local regulatory agency to terminate the study

4.7 Accountability procedures for the investigational products

Study drug will be dispensed by the pharmacy at the investigator's institution. The patient may be dispensed up to an 8 weeks supply of medication. The pharmacy must maintain an individual record of the patient. Drug dose, number of tablets received and returned must be recorded.

5 Selection and Withdrawal of Subjects

5.1 Inclusion Criteria

1. Heart failure patients with reduced ejection fraction (EF≤40%) as assessed by echocardiographyat least 6 months prior to recruitment and NYHA Class≥2
2. Patients implanted with ICD, CRTD/S or CRTP devices that are capable of recording the PVC burden and implanted ≥ 2 months prior to recruitment.
3. High risk for arrhythmic events at baseline identified by either PVC burden ≥2% **or** ≥2 events of non sustained VT **or** ≥1 event of sustained ventricular tachycardia **or** need for anti-tachycardia pacing **or** defibrillation therapy, during a period of 2 months prior to recruitment.
4. Diagnosis of type 2 diabetes mellitus prior to informed consent
5. HbA_1c≥7% and ≤12%.
6. Signed and dated written informed consent by date of Visit 1 in accordance with GCP legislation.

5.2 Exclusion Criteria

1. Evidence of ICD malfunction.
2. Antiarrhythmic treatment other than beta blockers.
3. Past exposure to SGLT2 inhibitors.
4. Uncontrolled diabetes with HbA1c>12% or glucose >240 mg/dL after an overnight fast.
5. Liver abnormalities defined by serum levels of alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase above 3 x upper limit of normal.
6. Planned cardiac procedure within 3 months.
7. Prior MI in the last 40 days.

8. Calculated eGFR< 45ml/min/1.73m2 as determined by the MDRD formula
   GFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)
9. BMI>50
10. Medical History of active cancer in the last 2 years. Exceptions include the following: Basal cell carcinoma of the skin, Squamous cell carcinoma of the skin, Carcinoma *in situ* of the cervix, Carcinoma *in situ* of the breast, Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b).
11. History of recurrent UTIs or genital infections
12. Systolic blood pressure<90mmHg.
13. Alcohol or drug abuse within 3 months of informed consent.
14. Pre-menopausal women (last menstruation <+ 1 year prior to informed consent) who:

    - are nursing or pregnant or

    - are of child-bearing potential and are not practicing an acceptable method of birth control, or do not plan to continue using this method throughout the study and do not agree to submit to periodic pregnancy testing during participation in the trial. Acceptable methods of birth control include tubal ligation, transdermal patch, intra uterine devices/systems, oral, implantable or injectable contraceptives, sexual abstinence, double barrier method and vasectomised partner.

15. Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial or participating in another trial involving an investigational drug and/or follow-up

5.3 Interruption or Discontinuation of Treatment

5.3.1 Discontinuation of study drugs

See section 4.4.1

5.3.2 Interruption of study drugs

No study drug interruption is allowed unless for safety reasons.

5.4 Study Discontinuation

See section 4.5

6 Treatment of Subjects

6.1 Treatment regimen

Patients will receive study drug: empagliflozin or placebo for an exposure period of up to 16 weeks - at the two treatment periods in a crossover design. Dosage, dosage regimen and route of administration are detailed in 4.3.1

6.1.1 Treatment assignment

This study will be double blind. At the Baseline/randomization visit, qualified patients will be randomly assigned in a 1:1 ratio to either empagliflozin at a dose of 10 mg/day or placebo (study drug packages will be identical for all treatments).

Each patient's treatment will be assigned manually on the basis of a pre-determined randomization schedule prepared by the data management of the study CRO (_____). The randomization code will be generated and stored under secure and blinded conditions. The randomization will include stratification logarithm by ischemic versus non-ischemic cardiomyopathy and PVC burden at screening of< or ≥ to 4%

Each subject will be assigned a subject screening number.

The screening number will be structured so that each subject participating in the study will have a unique number. Screening number must not be re-used for different subjects. In case a subject is re-screened, the initial screening number should be retained and used.

Once subject's eligibility is confirmed, a subject will be assigned with a unique randomization number and will be randomized to treatment arm according to the randomization list Randomization number which will start with an RND or ENR followed by the site number and 3 digit subject number (for example – RND/ENR01-001, RND/ENR01-002 etc. for site number 1, etc.)

A dedicated "Subject Identification Log" will be kept at site. This log will include the subject's identifying details (e.g. name, ID number, telephone number) together with the screening and randomization number (if applicable).

The "Subject Identification Log" will be kept only at the investigational site and will not be taken out of the site.

6.2 Concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate Case Report Form. The administration of antiarrhythmic treatment other than beta blockers

is NOT permitted. Similarly, the use of other concurrent investigational drugs is not allowed. The use of any of the prohibited medications or drugs/illegal substances within the prohibited time period will be considered a protocol deviation, which must be recorded on the appropriate CRF(s) or deviation violation form. Subjects with repeated protocol deviations may be discontinued from the study at the discretion of the investigator and/or sponsor.

6.3 Treatment compliance

Number of study drug tablets administrated orally to every subject at home, will be evaluated by blister check up by the study coordinator/investigator and accounted on CRF.

7 Assessment of Efficacy

Efficacy assessments will be evaluated by: PVCs burden, NSVT number, Composite endpoint of: number of sustained VT+VF, ATP or delivery of shock therapy, BNP, End diastolic diameter and ejection fraction.

7.1 PVCs Burden

The primary efficacy parameter to be assessed will be PVCs burden.

PVCs burden is defined as the PVCs percentage of all beats in a pre-specified period captured on ICD or CRTD/P device.

PVCs burden will be evaluated as a part of the device interrogation on visit 1 to assess device integrity and proper function, in visit 2 to assess patient's eligibility for the study according to in- and exclusion criteria. In visits 3 and 5 to assess for treatment efficacy.

Assessment of the PVCs will be based on PVC counters for the various ICD/CRTD/P interrogated (from Medtroinic, St. Jude, Guidant – Boston Scientific, Biotronik). Monitor counter reset will be conducted on visit 1,2,3,4 and 5. The equation for calculating the PVC burden for monitoring providing the PVC number per period will be:

$$PVC\ Burden(\%) = \frac{Number\ of\ PVCs}{Average\ HR\ \left(\frac{beats}{minute}\right) * 60 * 24 * (\#days\ in\ the\ period\ assessed)}$$

For monitors providing the PVC burden per hour the calculation will be:

$$PVC\ Burden(\%) = \frac{Average\ \frac{PVC}{hour}}{Average\ Heart\ Rate(\frac{Beats}{Minute}) * 60}$$

In case of device malfunction, counter malfunction or any other cause of inability to readout the device PVC counter measurement, PVC burden will be

calculated from a 12 Lead ECG Holter for 24 hours conducted at one of the last 7 days of the period assessed and will be calculated as:

$$PVC\ Burden(\%) = \frac{Number\ of\ PVCs}{Average\ Heart\ Rate\ \left(\frac{beats}{minute}\right) * 60 * 24}$$

Monitor counter readout and resetting will be performed by an electrophysiologist technician; data will be entered into the CRF by the study coordinator after approval of the principal investigator.

7.2 Non-sustained ventricular tachycardia (NSVT)

Non-sustained ventricular tachycardia number is defined as the NSVT number in a pre-specified period captured on ICD or CRTD/P device interrogation, or as a backup information (in case of ICD or CRTD/P malfunction) on Holter ECG. The device will be activated during the whole study period and data will be captured on the CRF at visits 1 to 5. The Holter ECG device of 24 h' will be performed in case of device malfunction, counter malfunction or any other cause of inability to readout the device PVC counter measurement. Holter assessment will be conducted at one of the last 7 days of the period assessed. Data from study device/Holter will be captured on the CRF at visits 2, 3 and 5.

.

7.3 A composite cumulative endpoint of ventricular arrhythmia load

This is defined as the number of sustained ventricular tachycardia, and/or ventricular fibrillation, and/or tachycardia pacing (ATP) and/or delivery of shock therapy. All the four parameters will be captured on ICD or CRTD/P device interrogation. Sustained VT and NSVT will be captured as a backup information (in case of ICD or CRTD/P malfunction) on Holter ECG. The device will be activated during the whole study period. The Holter ECG device of 24 h' will be performed In the case of device malfunction, counter malfunction or any other cause of inability to readout the device PVC counter measurement. Holter

assessment will be conducted at one of the last 7 days of the period assessed. Data from study device/Holter will be captured on the CRF at visits 2, 3 and 5.

7.4 NT-Pro-BNP

NT-Pro-BNP Is a plasma level of B-type Natriuretic Peptide used as a blood test for diagnosing and evaluation the presence/severity of heart failure. Plasma level will be performed at visits:2 to 5.

7.5 Left ventricular end diastolic diameter

End diastolic diameter is defined as the cross-sectional diameter of the left ventricle, including the septum and the posterior thicknesses in diastole. The assessment is performed by echocardiography done at visits: 1 to 3 and 5.

7.6 Left ventricular ejection fraction (EF)

Ejection fraction is defined as the ratio of the stroke volume to the end-diastolic volume in the left ventricle as performed by echocardiography and expressed by percentage. The assessment is performed by echocardiography done at visits: 1 to 3 and 5.

8 Assessment of Safety

Safety assessments will consist of evaluating adverse events and serious adverse events, adverse events of special interest, laboratory parameters including hematology, chemistry & urine analysis, vital signs, physical examinations, monitoring compliance, and documentation of all concomitant medications and/or therapies.

8.1 Adverse events

The information obtained during study visit subject questioning, review of subject's compliance record, physical examinations, vital signs measurements, blood testing, and by any other means will be evaluated in light of baseline medical data and thus provide the basis for adverse events identification and grading. The adverse events reported during the trial will be graded (see 8.1.3 below), documented and assessed in light of their clinical significance and relation to investigational product. In addition, the following information regarding the AE must be obtained: start date, end date (if applicable), outcome (resolved / unresolved), and action taken (e.g. dose adjustment, therapy discontinuation, concomitant medication). Adverse event monitoring will be conducted throughout subject's participation.

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Clinical events occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms leading to a premature control of the abnormal value before the next scheduled laboratory test, leading to a change in study medication (e.g. dose

modification, interruption or permanent discontinuation), requires a change in concomitant therapy (e.g. addition or change in a concomitant medication, therapy or treatment) or require therapy.

Any Adverse Event occurring by the time of study completion (within four weeks of last drug intake) must be recorded on the Adverse Event CRF page.

Any adverse event term needs to be provided for each event; preferably using the short name based on the CTCAE ver. 4.0 or preferred term on the MedDRA.

8.1.1 Definitions of adverse events

Adverse event

An adverse event is defined as any untoward medical occurrence or effect in a patient treated on a study protocol, which does not necessarily have a causal relationship with the study treatment. An AE is therefore described as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study treatment, whether or not considered related to the study treatment. This definition includes any abnormalities or anomalies that were not seen at baseline or which worsened during the course of the study, if present at baseline.

Adverse Reaction (AR)

This is defined as **all untoward and unintended responses to a study treatment related to any dose administered.** A causal relationship between the study treatment and an AE is at least a reasonable possibility (probably or possibly related), i.e. the relationship cannot be ruled out.

Serious Adverse Event

A serious AE (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening AE, as defined below
- patient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity

- a congenital anomaly/birth defect
- important medical event, as defined below

A life-threatening AE is any AE that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death).

An important medical event is an AE that may not result in death, be life-threatening, or require hospitalization but may be considered a serious AE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. It can also include AEs otherwise judged to be serious by either the investigator or the sponsor.

8.1.2 Adverse events of Special Interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the Pharmacovigilance Department of Boehringer Ingelheim within the same timeframe that applies to SAEs.

Patients with AESIs need to be followed up appropriately, regardless of the origin of the laboratory data (e.g. central, local etc.). The Investigator should consider which, if any, concomitant therapies should not be taken during evaluation. Discontinued treatments can be reintroduced per Investigator discretion.

The following are considered as AESIs:

<u>Hepatic injury</u>

A hepatic injury is defined by the following alterations of hepatic laboratory parameters after randomisation:

- an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood sample
- an isolated elevation of ALT and/or AST ≥ 5 fold ULN

These laboratory findings constitute a hepatic injury alert and the patients showing these abnormalities need to be followed up according to medical judgement. .

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test.

Decreased renal function

Decreased renal function is defined by a creatinine value showing a ≥ 2 fold increase from baseline and is above the ULN.

For the AESI “decreased renal function”, the Investigator shall collect an unscheduled laboratory sample for creatinine as soon as possible and initiate follow-up laboratory tests of creatinine according to medical judgement.

Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)

In case of metabolic acidosis, ketoacidosis and DKA further investigations should be done according to the medical judgment and the clinical course until a diagnosis is made and/or the patient is recovered.

DKA is defined by the diagnostic criteria in the table below, and as defined by the American Diabetes Association (ADA).

Investigators should note that not all criteria in the table below need to apply for the diagnosis of DKA, and clinical judgment should also be taken into consideration. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated in the table below.

Table 3 Diagnostic criteria for DKA

Table 3 Diagnostic criteria for DKA

	DKA		
	Mild	Moderate	Severe

Plasma glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25-7.30	7.00-7.24	<7.00
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10
Urine ketones*	Positive	Positive	Positive
Serum ketones*	Positive	Positive	Positive
Effective serum osmolality (mOsm/kg)**	Variable	Variable	Variable
Anion gap***	>10	>12	>12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma

* Nitroprusside reaction method

** Calculation: 2[measured Na (mEq/L) + gluc

Contact details of the local pharmacovigilance unit/LVPM: E-mail: PV_local Israel@boehringer_ingelheim.com

Suspected Unexpected Serious Adverse Reaction (SUSAR) This is defined as an adverse reaction, the nature or severity of which is not consistent with the known study treatment information.

8.1.3 Adverse events grading

AE will be documented and graded according to the International Common Toxicity Criteria (CTCAE) version 4.0

AE that do not appear in the CTC will be graded as follows:

- Mild (Grade 1): Sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities
- Moderate (Grade 2): Sign or symptom, which may be ameliorated by simple therapeutic measures, may interfere with usual activity.
- Severe (Grade 3): Sign or symptom that is intense or debilitating and that interferes with usual activities and/or requires hospitalization. Recovery is usually aided by therapeutic measures and the discontinuation of the study product may be required.

- Life threatening or disabling (Grade 4): Sign or symptom that is Life threatening or disabling.
- Death (Grade 5): Death related to AE

8.1.4 Adverse events outcome

Outcome is classified as follows:

1. Recovered – The subject has fully recovered from the AE with no residual effects observable.
2. Recovered with sequelae – The subject has fully recovered from the AE with residual effects.
3. Ongoing – AE is still ongoing by the end of study.
4. Unknown.
5. Death.

8.1.5 Causality Assessment of Adverse events

All AEs will be evaluated by the investigator and assigned an estimated relationship to the investigational product. As empagliflozin safety profile is well established, the investigator should consider it when evaluating AE relationship to empagliflozin. The terms "probable", "possible", "remote", or "unrelated" refer to the association with the use of the investigational product, as defined below.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Assessment of causal relationship should be recorded directly in participant CRF.

AEs associated with the use of investigational product

AEs associated with the use of investigational product (i.e. probably or possibly related to treatment as defined below) are also termed Adverse Drug Reactions (ADRs).

Probable: AE that are considered with a high degree of certainty to be related to the investigational drug. An AE is considered probably related if:

- It follows a reasonable temporal sequence to the administration of the drug.
- It cannot be reasonably explained by the known characteristics of the patient subject's clinical state, environmental factors, or other modes of therapy administered to the subject.
- It follows a known pattern of response to the drug.

Possible: AE in which the connection between the investigational drugs appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if:

- It follows a reasonable temporal sequence to the administration of the drug.
- It may have been produced by the patient's clinical state, environmental factors, or other modes of therapy administered to the patient.
- It follows a known pattern of response to the drug.

AEs not associated with the use of investigational product

Remote: AE that meet the following criteria:

- It does not follow a reasonable temporal sequence to the administration of the drug.
- It may readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy administered to the subject.
- It does not follow a known pattern of response to the drug.

Unrelated: AE that are judged to be clearly and incontrovertibly due only to extraneous causes, and do not meet the criteria for Probable, Possible, or Remote defined above.

8.2 Adverse events reporting and monitoring requirements

8.2.1 General

All adverse events, serious and non-serious, will be fully documented in both source documents and CRF, and each AE will be assessed in light of its clinical significance. For each adverse event, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken with the investigational drug. The investigator will determine the relationship to the investigational drug, i.e. causality assessment, for each AE.

Events occurring prior to initiation of first dose should be recorded on the Medical History page of the CRF. Any AE occurring after initiation of the first dose and/or during any point throughout the study should be recorded on the Adverse Event page of the CRF. All adverse events occurring up to 30 days after the last dose of study drug administration should be captured in the CRF. AEs should be recorded in the CRF using the CTC AE terminology (short name). Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology.

Occurrence of any grade 4 AE must warrant clinical evaluation by the treating investigator to decide whether it is considered an SAE. If it is an SAE the investigator should report it to the sponsor within 24 hours (see section 8.2.2 SAE Reporting). Grade 4 AEs, which were not considered SAEs by the investigator, should be reviewed by the monitor who will forward them to the sponsor's medical monitor to approve that none of the AEs are SAEs.

8.2.2 SAE reporting

The PI or his designee must report to the sponsor any SAE or AESIs independent from their seriousness, if applicable occurring after first dose of study drug and up to 30 days after last dose of study drug, regardless of their relationship to the investigational product.

Sponsor contact details for SAE reporting:

Reports concerning SAEs and AESIs, if applicable, and pregnancy reports shall be forwarded to the BI Unique Entry Point in accordance with the following timelines:

(i) Initial and follow-up reports concerning SAEs and AESIs, if applicable containing at least one (1) fatal or immediately life-threatening event within five (**1**) calendar days upon receipt,

(ii) Initial and follow-up reports of any other SAE and AESI, if applicable within ten (1) calendar days upon receipt.

(iii) Pregnancy report and outcome of pregnancy within seven (3) calendar days upon receipt.

The SAE reports shall include all SAEs, AESIs (if applicable) and non-serious AEs which are relevant for the reported SAE or AESI and, in particular, the following information:

(i) the listedness of the reported events based on BI Investigator's Brochure for the Study Drug or BI Drug Information e.g. Summary of Product Characteristics (SmPC) or Product Information (PI) for the authorized Study Drug provided by BI,

(ii) Investigator's causal assessment as to whether the event(s) is/are related to the use of the Study Drug, and

(iii) the seriousness of each AE.

An initial report shall be completed in a Serious Adverse Event form provided by the sponsor and must be faxed or emailed to rmarilus@netvision.net.il, fax: 972-9-9540457 within 24 hours of the investigator becoming aware of the event, and must include SAE general description, start date, end date (if applicable), the reason for evaluation as a SAE, basic patient information, assessment of the relationship to the investigational product, expectedness, and study therapy information.

When new, updated, or corrected information about a previously reported SAE is obtained, the SC should fill out a follow-up report and fax or email it to

the sponsor within 48 hours of receiving the FU information. Relevant concomitant medication and medical history CRF pages shall be included in the Follow-up report. Source documents to support the SAE (e.g. discharge summary, test results) shall be included as well.

The SAE form used to document an SAE FU is the same form used to document an SAE.

A complete SAE report (i.e. With no missing information) must be sent to the sponsor at the first possible date and no later than 7 calendar days after SAE end date.

SAE will be recorded on designated CRF forms in a timely manner and no later than 7 calendar days after its end date.

Where a SAE is followed by reports of recurrent episodes, re-exposure, complications or progression of the initial SAE, all such reports must be reported as follow-up to the original episode. If a new SAE occurring at a different time interval is considered completely non-associated to a previously reported one, a new SAE form should be submitted as an initial report.

The PI or his designee will submit the SAE report to IRB/EC according to applicable local regulations.

8.2.3 Expedited Reporting

Expedited reporting by PI to IRB/EC is warranted for all Suspected Unexpected Serious Adverse Reactions (SUSAR), i.e. unexpected SAEs that are considered related to study product as defined in Section 8.1.5. Additional cases will be communicated by PI to IRB/EC via expedited reporting when required by local regulation.

Any SAE, irrespective of causality, occurring in a patient after providing informed consent and until four weeks after ending study participation / study drug administration must be reported. SAEs occurring afterwards should only be reported if considered by the investigator attributable to the sponsor investigational drug(s).

8.2.3.1 Sponsor Reporting SUSARs to PI

The sponsor should report all Suspected Unexpected Serious Adverse Reactions (SUSARs), i.e. unexpected SAEs that are considered related to study product as defined in Section 8.1.1, to the PI in the following timelines: death and other life threatening events will be reported within 7 days of the date the event was reported to sponsor and the rest of the SUSARs will be reported to the PI within 15 days. The sponsor should provide the PI with the list of SUSARs that occurred in all of the sites periodically, at least once every 6 months. The report will include a summary of the main safety issues of the study product that came up during the reporting period.

8.2.3.2 Reporting SUSAR to the Israeli MOH

The sponsor should report SUSARs to the Israeli MOH in an annual Development Safety Update Report (DSUR), which describes all of the new safety information accumulated during the year. The report should include a summary and conclusions of the main safety issues of the study product.

The DSUR should be sent to dsur@moh.health.gov.il within 60 days of the data lock. In addition, the sponsor should send the MOH the DSUR on a CD with an accompanying letter. The sponsor should inform the PI and the MOH of the following information within 7 days of receiving it:

a. Decisions of regulatory authorities regarding the continuation of the study
b. Any decision to discontinue the study for any reason, temporarily or permanently.

All notifications to the MOH should be sent to:

clinicaltrials.pharm@moh.health.gov.il

Any pregnancy of a study subject or a partner of a male subject after the first dosing is considered an immediately reportable event.

Such events must be reported within one (1) working day of the investigator becoming aware of the event. Pregnancies shall be followed for the duration of the pregnancy. It is the PI's responsibility to provide to the sponsor follow-up

information on the outcome of the pregnancy including information about any sequelae.

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form.

Additional safety examinations and procedures

If any unclear clinical event, including symptoms, signs, or other observations or abnormalities, should occur, the Investigator, or any other physician in charge, may perform additional clinical examinations and procedures (other than outlined in this protocol), including any clinical, laboratory, imaging and/or technical testing, in order to clarify and establish the etiology and diagnosis of this clinical event.

8.3 Pregnancies

Any pregnancy of patient or patient's spouse that occurs during study participation should be reported using a Clinical Trial Pregnancy Form. To ensure patient safety each pregnancy must also be reported to the sponsor and BI within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities or maternal and newborn complications.

8.4 Laboratory evaluations

Laboratory results will be reported to the investigator who will review abnormal laboratory findings for clinical significance. The investigator will document any laboratory test results that are clinically significant on the lab report and provide details of the relationship to investigational product and the action taken. If a change in a laboratory value represents a medical condition, the medical condition will be listed in the AE record unless this is a pre-existing medical condition allowed under the inclusion criteria. If no correlation is possible, the direction of change (increase or decrease) and the actual value will be recorded.

The institution will perform laboratory analyses according to the Visit Schedule (see Table 2). The sponsor must be provided with a copy of the laboratory's certification, and a tabulation of the normal ranges for each parameter required. Additionally, if at any time a patient has laboratory parameters obtained from a different outside laboratory, the sponsor must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g. require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate Comment CRF page in addition to the appropriate laboratory CRF page. When abnormal laboratory values or test results constitute an adverse event (i.e., induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events CRF.

8.4.1 Hematology

Hematology includes assessment of Complete Blood Count (CBC) including: hemoglobin, white blood cell count, platelet count, and a differential count including: neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Hematological evaluations (CBC) should be collected according to the Visit Schedule (see Table 2).

8.4.2 Biochemistry

The following blood chemistry results should therefore be collected according to the Visit Schedule (see Table 2).

Serum Creatinine, Bun, Glucose, Sodium, Potassium, Total Protein, Albumin, SGOT (AST), SGPT (ALT), Alkaline Phosphatase, and Total Bilirubin.

When, in the opinion of the investigator, other clinical laboratory evaluations may be relevant for assessing the patient's status, they will be completed and entered into the database as appropriate.

8.4.3 Special tests:

N/A

8.4.4 Urinalysis

Urinalysis will be performed according to the visit schedule (see Table 2). Specific gravity, pH, semi-quantitative “dipstick” evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood. In case of findings on the urinary dipstick, such as leukocytes, nitrites or blood (except during menstruation for the female subjects), a microscopic examination including RBC/HPF, WBC/HPF and casts/LPF will be performed. If casts are noted, the type is to be specified on the relevant comments page in the CRF. A midstream urine sample (~ 30 mL) will be obtained, in order to avoid contamination and allow a proper assessment.

8.5 Physical examinations/vital signs

A physical examination including vital signs will be performed according to the Visit Schedule (see Table 2). Information about the physical examination and vital signs must be present in the source documentation at the study site. Significant findings present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions CRF. Significant findings made after the start of study drug, which meet the definition of an adverse event, must be recorded on the Adverse Event Case Report Form. There are no Case Report Forms to capture routine normal findings from physical examinations and vital signs assessments. Vital signs will include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), systolic and diastolic blood pressure (mmHg).

9 Statistics

9.1 Sample size

The primary endpoint is the percentage of PVCs during the 2 months of empagliflozin treatment compared with the percentage of PVC on placebo. A sample size of 128 patients was selected based on the estimated effect of 10% reduction in the rate of arrhythmic events assuming a standard deviation of 40% in measured values, with alpha of 0.05 and power of 0.8 (2-sided test). The efficacy analysis will be conducted using an as treated approach and will be performed using the Wilcoxon signed-rank test, p value≤0.05 will be considered significant.

The rationale for sample size calculation was based on detecting a difference of at least 10% in the reduction in rate of arrhythmic events from baseline between study treatments with 80% power and 5% significance level.

Sample size justification

When the sample size in each sequence group is 64, (a total sample size of 128) a 2 x 2 crossover design will have 80% power to detect a difference in Mean reduction of -10.0, assuming that the Crossover ANOVA MSE is 28.284 (the Standard deviation of differences, sd, is 40.0) using a two group T-test (Crossover ANOVA) with a 0.05 two-sided significance level.

Reference:

Senn, Stephen Cross-over Trials in Clinical Research (2nd Edition) Wiley (2002).

9.2 Efficacy and Safety evaluation

General

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics.

For categorical variables, summary tables will be provided giving sample size, absolute and relative frequency and 95% CI (Confidence Interval) for proportions by study treatment.

For continuous variables, summary tables will be provided giving sample size, arithmetic mean, standard deviation, median, minimum and maximum and 95% CI (Confidence Interval) for means of variables by study treatment.

All tests will be two-tailed, and a p value of 5% or less will be considered statistically significant.

The data will be analyzed using the SAS ® version 9.3 (SAS Institute, Cary North Carolina).

Analysis Populations

Safety Population: will include all randomized subjects who received any study drug.

Intention-to-Treat (ITT) Population: will include all subjects included in the safety population who provided at least one post-baseline assessment for the primary endpoint.

Per-Protocol Population: will include all subjects in the ITT population who complete the study in compliance with the protocol and have no major protocol violations.

9.2.1 Efficacy analysis:

The primary endpoint is the percentage of PVCs during the 2 months of empagliflozin treatment compared with the percentage of PVC on placebo.

The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the carry-over effect in the primary endpoint between the two sequences.

If no carry-over effect will be observed, then The Paired T-test or non-parametric Signed-rank test for two means (as is appropriate) will be applied for analyzing the difference in the above changes between the tested treatment and placebo.

Otherwise, if a carry-over effect will be found statistically significant, then the MMRM model (Mixed-effect model for repeated measures) will be applied for analyzing the difference in the above reduction between the tested treatment and the placebo. The model will included terms for study arm (sequence), treatment and period as fixed effects, and subject nested within study arm as a random effect. Other covariates (such as age and baseline measures) will be included if they will be found different between the groups and affecting the outcome.

<u>Secondary Endpoints:</u>

Frequency of non-sustained ventricular tachycardia (NSVT) episoedes and composite cumulative ventricular arrhythmia load will be summarized by treatment.

Changes in blood level of NT-Pro Brain Natriuretic peptide (BNP), Left ventricular end diastolic diameter and Left ventricular ejection fraction (EF) from baseline will be summarized in appropriate tables by treatment.

9.2.2 Safety Analysis:

Data from all subjects who receive any study drug will be included in the safety analyses.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, most updated Version) terminology and presented in tables by System Organ Class (SOC) and Preferred Term (PT).

AE data will be listed individually and summarized by SOC and by PT within a system organ class under each treatment.

The severity of the toxicities will be graded according to the NCI CTCAE (Ver4.0) whenever possible. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events will be summarized by worst NCI CTC grade. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE Grade 3 or Grade 4, study-drug-related events, and serious adverse events will be summarized separately.

Laboratory data will be graded according to NCI CTCAE severity grade.

Any deviations from the previously described statistical plan will be described and justified in a protocol amendment.

Other safety parameters including vital signs and physical examination will be summarized in appropriate tables.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

10 Direct Access to Source Data/Documents

Access to the subject's source data and study documents will occur only with the subject's acknowledgement and agreement by signing an informed consent. The investigator will permit study-related monitoring, audits, Institutional Review Board (IRB) review and regulatory inspection(s), providing direct access to source data and documents.

10.1 Study monitoring

The monitoring visits will enable the sponsor or the monitor acting on his behalf, to assess the study's progress status, to verify the exactness and degree of completeness of the CRFs, to ensure that protocol as well as local regulations are being followed and that the investigator is fulfilling his obligations. Monitoring visits will also enable to correct errors in the CRFs compared to the source documents. The investigator will authorize the monitor, at a mutually convenient time during the study and after its end, to periodically review all of the CRFs and the related parts of administrative, medical and laboratory files of each participant in the study. The CRFs must be filled out before the monitoring visits.

10.2 Audits

During the study, people belonging to the sponsor quality assurance group may visit the investigator site in order to audit the study. The purpose of this visit is to check that the study is carried out according to Good Clinical Practices. Before conducting an audit, the monitor will contact the investigator in order to agree upon a mutually suitable date. The investigator and his team are required to cooperate with the auditors and to grant them access to the patients' medical files and to the study documents (CRFs and investigator's binders).

10.3 IRB and regulatory inspections

A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a regulatory authority, the investigator must inform the sponsor and BI immediately that this request has been made.

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

11 Quality Control and Quality Assurance

Data from the CRFs are entered into the study database by Contract Research Organization staff following their own internal standard operating procedures that have been reviewed and approved by the sponsor.

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by Data Management personnel. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to the sponsor so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

12 Ethics

12.1 Institutional Review Board

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board (IRB). A signed and dated statement that the protocol and informed consent have been approved by the IRB must be given to the sponsor before study initiation. The name and occupation of the chairman and the members of the IRB must be supplied to the sponsor. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

12.2 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered part of the protocol, and must be submitted by the investigator with it for IRB approval.

12.3 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki, which can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

13 Data Handling and Record Keeping

The information resulting from the execution of the protocol will be coded into the eCRFs database.

The eCRFs must be filled out on a timely basis. The data will be monitored and verified.

Each eCRF will be signed and dated by the investigator or a co-investigator named by the former in each site and clinically responsible for the patient during the study.

Access to the eCRF will be by individual passwords & according to GCP recommendations.

The completed eCRFs data will be transferred by the eCRF operator to the sponsor & will be kept by them for at least 15 years.

14 Financing and Insurance

Financing and insurance will be addressed in the future in a separate agreement.

15 Publication Policy

Any formal presentation or publication of data from this trial will be considered as a joint publication by the investigator(s) and appropriate sponsor's personnel. Authorship will be determined by mutual agreement. It is a multicenter study, it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol, by the sponsor statisticians, and not by the investigators. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full publication, unless formally agreed to by all other investigators and the sponsor.

The investigator may be required to sign the clinical study report, if it is to be used in a registration submission to the health authorities of some countries. For multicenter studies, only the coordinating (principle) investigator nominated by the sponsor at the start of the trial would provide any needed signature.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *The New England journal of medicine*. 2015;373:2117-2128
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes research and clinical practice*. 2010;87:4-14
3. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: Cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation*. 2016;134:752-772
4. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. *Annals of internal medicine*. 2013;159:262-274
5. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *The New England journal of medicine*. 2016;375:323-334
6. Ferrannini E, Seman L, Seewaldt-Becker E, Hantel S, Pinnetti S, Woerle HJ. A phase iib, randomized, placebo-controlled study of the sglt2 inhibitor empagliflozin in patients with type 2 diabetes. *Diabetes, obesity & metabolism*. 2013;15:721-728
7. Cleland JG, Chattopadhyay S, Khand A, Houghton T, Kaye GC. Prevalence and incidence of arrhythmias and sudden death in heart failure. *Heart failure reviews*. 2002;7:229-242
8. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *The New England journal of medicine*. 2008;359:1009-1017
9. Mark DB, Anstrom KJ, Sun JL, Clapp-Channing NE, Tsiatis AA, Davidson-Ray L, et al. Quality of life with defibrillator therapy or amiodarone in heart failure. *The New England journal of medicine*. 2008;359:999-1008
10. Aktas MK, Mittal S, Kutyifa V, McNitt S, Polonsky B, Steinberg J, et al. The burden and morphology of premature ventricular contractions and their impact on clinical outcomes in patients receiving biventricular pacing in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (madit-crt). *Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc*. 2016;21:41-48
11. Ataklte F, Erqou S, Laukkanen J, Kaptoge S. Meta-analysis of ventricular premature complexes and their relation to cardiac mortality in general populations. *The American journal of cardiology*. 2013;112:1263-1270
12. Cheriyath P, He F, Peters I, Li X, Alagona P, Jr., Wu C, et al. Relation of atrial and/or ventricular premature complexes on a two-minute rhythm strip to the risk of sudden cardiac death (the atherosclerosis risk in communities [aric] study). *The American journal of cardiology*. 2011;107:151-155

13. Kostis JB, Byington R, Friedman LM, Goldstein S, Furberg C. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. *Journal of the American College of Cardiology*. 1987;10:231-242

14. Lee V, Hemingway H, Harb R, Crake T, Lambiase P. The prognostic significance of premature ventricular complexes in adults without clinically apparent heart disease: A meta-analysis and systematic review. *Heart (British Cardiac Society)*. 2012;98:1290-1298

15. Lerma C, Gorelick A, Ghanem RN, Glass L, Huikuri HV. Patterns of ectopy leading to increased risk of fatal or near-fatal cardiac arrhythmia in patients with depressed left ventricular function after an acute myocardial infarction. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2013;15:1304-1312

16. Martinez-Alanis M, Ruiz-Velasco S, Lerma C. Quantitative analysis of ventricular ectopic beats in short-term rr interval recordings to predict imminent ventricular tachyarrhythmia. *International journal of cardiology*. 2016;225:226-233

17. Mittal S, Aktas MK, Moss AJ, McNitt S, Kutyifa V, Steinberg JS, et al. The impact of nonsustained ventricular tachycardia on reverse remodeling, heart failure, and treated ventricular tachyarrhythmias in madit-crt. *Journal of cardiovascular electrophysiology*. 2014;25:1082-1087

18. Ruwald MH, Mittal S, Ruwald AC, Aktas MK, Daubert JP, McNitt S, et al. Association between frequency of atrial and ventricular ectopic beats and biventricular pacing percentage and outcomes in patients with cardiac resynchronization therapy. *Journal of the American College of Cardiology*. 2014;64:971-981

19. Dukes JW, Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS, et al. Ventricular ectopy as a predictor of heart failure and death. *Journal of the American College of Cardiology*. 2015;66:101-109

20. Ruskin JN. The cardiac arrhythmia suppression trial (cast). *The New England journal of medicine*. 1989;321:386-388

21. Goldstein S, Brooks MM, Ledingham R, Kennedy HL, Epstein AE, Pawitan Y, et al. Association between ease of suppression of ventricular arrhythmia and survival. *Circulation*. 1995;91:79-83

22. Zang M, Zhang T, Mao J, Zhou S, He B. Beneficial effects of catheter ablation of frequent premature ventricular complexes on left ventricular function. *Heart (British Cardiac Society)*. 2014;100:787-793

23. Santangeli P, Marchlinski FE. Ventricular ectopy as a modifiable risk factor for heart failure and death: "Deja vu all over again" may be a good thing. *Journal of the American College of Cardiology*. 2015;66:110-112

16 Supplements

Appendix 1 Diabetes medication titration

Researches will make an effort to prevent hypoglycemia events and worsening hyperglycemia at all stages of the study. All patients will receive an endocrinology consultation on diabetes medication titration prior to starting any study medication. Any changes in the diabetes treatment regimen are allowed apart from initiating SGLT2 inhibitors.
The consultation will include instruction to monitor fasting glucose closely on the first week of each period of the study, to make changes in medication doses upon initiation of each study period (including a specific recommendation for the washout period) and in any case that glucose is over 150 for 3 consecutive days (see details on specific medication below). This instruction will be repeated by the cardiologist on subsequent visits at the beginning of washout and at the beginning of the second treatment period.
If at any point of the study fasting glucose is over 180 for 7 days despite taking the following measures – schedule emergency endocrinology consultation within a week.

Decision to titrate depends on patient glycemic control prior to study:

A. Patients with HbA1c over 7.5% and fasting glucose usually over 150 with no hypoglycemia events or glucose measurements under 90 – no change in diabetes medications or insulin.

B. Patients with fasting glucose usually under 150 or HbA1c under 7.5% - when oral medication (empagliflozin or placebo) is started reduce insulin by 20%, stop sulfonylurea and repaglinide, titrate as indicated below according to glucose measurements.

Basal insulin

If fasting glucose usually under 150 or HbA1c under 7.5% - reduce by 20% upon initiation of study medication. Otherwise no change.

Further titration by the patient throughout study:

If fasting glucose for 3 days is: Basal insulin should be changed by:

>180 mg/dL → increase by 4 units

>140 mg/dL → increase by 2 units

<110 mg/dL -> decrease by 2 units

<100mg/dL → decrease by 4 units

If fasting glucose in even one measurement is low, reduce basal insulin:

<90mg/dL → decrease by 4 units

< 80 mg/dL → decrease by 6 units

Prandial insulin or insulin mixes

If preprandial noon/evening/bedtime glucose is under 100 - decrease all doses by 20%

If noon+evening+bedtime glucose is over 150 for 3 days – increase dose by 10%

Sulfonylurea

If fasting glucose under 150 mg/dL or HbA1c under 7.5% - stop

Then:

If fasting glucose over 150 for 7 days restart at half dose

If under half dose fasting glucose over 150 for 7 days - return to full dose

If anytime during study glucose under 90+symptoms or under 70 without symptoms – stop

Acarbose, DPP4 inhibitors, short acting GLP1 agonits

No initial changes

If hypoglycemia occurs (glucose under 90+symptoms or under 70 without symptoms) stop one medication in the following order: GLP1 agonist/DPP4 inhibitor, acarbose

Metformin ,

No initial changes.

If hypoglycemia only on Metformin and study drug – reduce Metformin to half the dose