

RESEARCH PROJECT

EFFECT OF DAPAGLIFLOZIN

ON NIGHTTIME BLOOD

PRESSURE IN TYPE 2 DIABETES

PROTOCOL NUMBER: DAPA-ESR-16-12460

EudraCT number:2017-002125-38

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0. SUMMARY

Title	Effect of dapagliflozin on nighttime blood pressure in type 2 diabetes
Protocol number	DAPA-ESR-16-12460
EudraCT number	2017-002125-38
Promotor	LM Diagnósticos S.L. C/ Castelló 117, 6 ^a planta, despacho 628.- 28006 Madrid
Principal	Julián Segura de la Morena
Investigator	Unidad de Hipertensión, Hospital Universitario 12 de Octubre, Madrid.
Coordinator	Luis Miguel Ruilope Urioste Grupo de Hipertensión Arterial y Riesgo Cardiovascular, Hospital Universitario 12 de Octubre.
Project office	ODDS SL
[CRO]:	C/ Wenceslao Fernández Flórez, 1 piso 2 •15005 A Coruña
Centres	Three university hospitals and the primary care centres in their area in Madrid (Clínico San Carlos, La Paz, 12 de Octubre)
Type of study	Randomized, multicentric, placebo-controlled, single-blind pilot study
Main outcome	Nighttime blood pressure in type 2 diabetic patients
Objective	To investigate the effect of the addition of 10 mg daily of dapagliflozin to the treatment of diabetic patients compared to the addition of placebo on the change in nighttime blood pressure (measured by ABPM) over 12 weeks among patients with albuminuria levels \geq 30 and $<$ 3000 mg/g creatinine and estimated glomerular filtration rate \geq 60 mL/min/1.73 m ² ..

Patients	225 patients with a previous diagnosis of type 2 diabetes and eGFR>30mL/min x1,73m ² , office BP above 140/70 mmHg, HbA1C 7.5-10%, albuminuria levels between 30 mg/g creatinine and 3000 mg/g creatinine and estimated glomerular filtration rate \geq 60 mL/min/1.73 m ² .
Intervention	10 mg once daily of dapagliflozin or placebo resembling dapagliflozin.
Chronogram	Administrative issues: 3 months (September-November2018) AEMPS/Ethical committee approval to first subject in: 1 month First subject in: December2018 50% enrollment: April 2019 Last subject in: June 2019 Last subject last visit: September2019 Recruitment of patients: 7 months (December2018-June 2019) Data cleaning and closing of the database: 3 months (october2019-December2019) Data analysis: 4 months (January 2020- April 2020) Final report and drafting of the manuscript: May 2020

1. INTRODUCTION

Cardiovascular (CV) disease is the leading cause of death worldwide, accounting for 30% of all deaths(1). High blood pressure (BP) is the most important individual factor contributing to global burden of disease worldwide (2), and as a consequence BP is the most important modifiable risk factor for CV disease. Prospective cohort studies have established a graded positive association between BP and the risk of CV disease, starting at 115 mmHg for systolic BP measured in the morning(3). The effectiveness of antihypertensive therapy was initially demonstrated in patients with systolic BP above 160 mmHg and the results of early prospective trials were reviewed two decades ago(4). More recently, the possibility of measuring BP out of the office has opened the investigation about the caveats of office BP measurements mainly consisting of white coat hypertension, masked hypertension, short-term BP variability, and nighttime BP, all these situations are characterized by an increase in CV and renal risk when compared to well controlled arterial hypertension(5, 6). The most relevant differences according to the accompanying risks is the one observed when daytime and nighttime BP levels are compared. Nighttime BP has shown to be the one accompanied by the highest level of risk when it is elevated(5). Data from the Spanish ABPM Registry(7) have shown that nighttime BP in albuminuric type 2 diabetics shows a significant difference when compared to values obtained in non-albuminuric type 2 diabetics. The same is true in non-diabetic patients with higher nighttime BP levels when albuminuria is present albeit not as much as in type 2 diabetics (7). According to our data, the differences in nighttime BP oscillates on average between 9-12 mmHg (7). Such a difference can account for the development of albuminuria as shown by Lurbe et al. type 1 diabetics(8). Both albuminuria and elevated nighttime BP are significant predictors of cardiovascular (CV) events and

deaths as well as of progression of chronic kidney disease (CKD)(5, 9), hence the control of nighttime BP could translate into a better CV protection and in a significant diminution of albuminuria if present.

The newest class of drugs for type 2 are the sodium glucose co-transporter 2 receptor (SGLT-2) inhibitors. These reduce the reabsorption of renal-filtered glucose back into the bloodstream, thereby leading to loss glucose in the urine. The Figure 1 obtained from Rajasekeran et al. (10) shows the main mechanisms of action of these drugs mediated mainly through glycosuria and natriuresis.

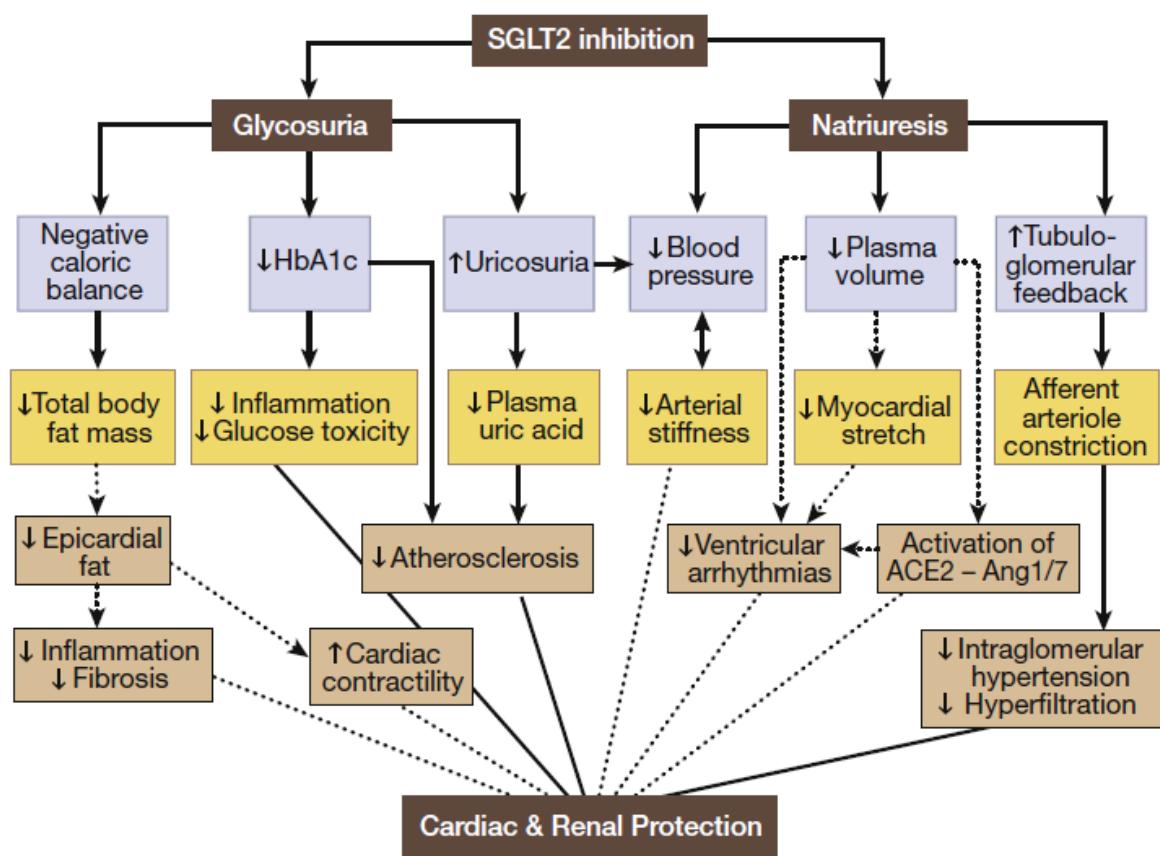


Figure 1. Cardiorenal protection of SGLT2 inhibitors mediated by glycosuria and natriuresis. Obtained from Rajasekeran et al.(10)

Other protective effect directly related to the heart improving left ventricular function and diminishing left ventricular mass have been described for these drugs(11, 12). Recently, the Empagliflozin Cardiovascular Outcome and Mortality in Type 2 Diabetes (EMPA-REG) trial(13) demonstrated the capacity of empagliflozin to significantly reduce the relative risk for both CV mortality and all-cause mortality as well as hospitalizations due to heart failure in type 2 diabetic patients. The study also demonstrated the capacity of the drug to slow the progression of kidney disease in type 2 diabetic patients together with the finding of a significantly lower risk of clinically relevant renal events(14).

SGLT2 antagonists are drugs with the capacity to lower BP above the level obtained by commonly used antihypertensive drugs(15).The decrease in BP contributes importantly to the good effects observed in EMPA-REG study(13).Dapagliflozin also improves significantly BP and does it during 24 hours(16).

We have hypothesized that the capacity of dapagliflozin to lower BP could be particularly intense during nighttime. This in turn could participate in the observed decay in albuminuria. Should this hypothesis be confirmed, it could contribute importantly to the potential positive influence of all SGLT2 in preventing mortality and hospitalization due to heart failure as shown by the EMPA-REG study(13).

2. OBJECTIVES

Primary Objective:

To investigate the effect of the addition of 10 mg daily of dapagliflozin to the treatment of diabetic patients compared to the addition of placebo on the change in nighttime blood pressure (measured by ABPM) over 12 weeks among patients with albuminuria levels ≥ 30 and < 3000 mg/g creatinine and estimated glomerular filtration rate ≥ 60 mL/min/1.73 m².

Secondary objectives:

- 1) To investigate the effect of the addition of 10 mg daily of dapagliflozin to the treatment of diabetic patients compared to the addition of placebo on the change in nighttime blood pressure (measured by ABPM) over 12 weeks in the subgroup of patients with high (30-300 mg/g creatinine) albuminuria levels.
- 2) To investigate the effect of the addition of 10 mg daily of dapagliflozin to the treatment of diabetic patients compared to the addition of placebo on the change in nighttime blood pressure (measured by ABPM) over 12 weeks in the subgroup of patients with very high (>300 mg/g creatinine) albuminuria levels.
- 3) Changes in albuminuria, office BP and HbA1C in the two subgroups of patients investigated

3. METHODS

This clinical trial will be conducted according to this Protocol, under the Regulation (EU) No 536/2014 and all regulatory requirements applicable to clinical trials and following the principles of Good Clinical Practice.

3.1. STUDY DESIGN

Type of study: Randomized, multicentric, placebo-controlled, single-blind pilot study.

3.2. PATIENTS

Type 2 diabetic patients recruited in the primary care setting in the area of three university hospitals in Madrid, irrespectively of the time since diagnosis and type of treatment received for their diabetes.

Entry criteria

- Patients with a previous diagnosis of type 2 diabetes and
 - Estimated glomerular filtration rate (eGFR) $\geq 60 \text{ mL/min} \times 1.73\text{m}^2$ and
 - Diagnosis of essential hypertension established at least one year before inclusion visit and suboptimal BP control (office BP above 140/70 mmHg)
 - HbA1C 7.5-10%
 - Albuminuria levels $\geq 30 \text{ mg/g}$ of creatinine

Exclusion criteria

- Age < 18 years old or ≥ 75 years old.
- Women of childbearing potential. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral

salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- Type 1 diabetes
- Albuminuria above 3000 mg/g of creatinine
- Established cardiovascular disease (stable heart failure, peripheral arterial disease or myocardial infarction or stroke within the previous 6 months)
- Intolerance to dapagliflozin
- On treatment with loop diuretic
- On treatment with SGLT2 inhibitors.
- On treatment with pioglitazone.
- Patients diagnosed of hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
- Patients who routinely work during nighttime (period between 11.00 p.m. and 7.00 a.m.)

3.3. DESCRIPTION OF THE INTERVENTION

The drug under evaluation, dapagliflozin, is approved to be used in adults who are 18 or older with type 2 diabetes mellitus for improving glycemic control and can be used in monotherapy when diet and exercise alone do not achieve good glycemic control and metformin use is not indicated due to intolerance, or in combination with other hypoglycemic agents, including insulin, when these, added to diet and exercise do not achieve good glycemic control. In this study it will be used in agreement with the terms in which its use is authorized.

The participants in the study, in addition to the treatment for their diabetes that were receiving from their attending physician, will receive 10 mg once daily of dapagliflozin or placebo resembling dapagliflozin. The randomization scheme follows below.

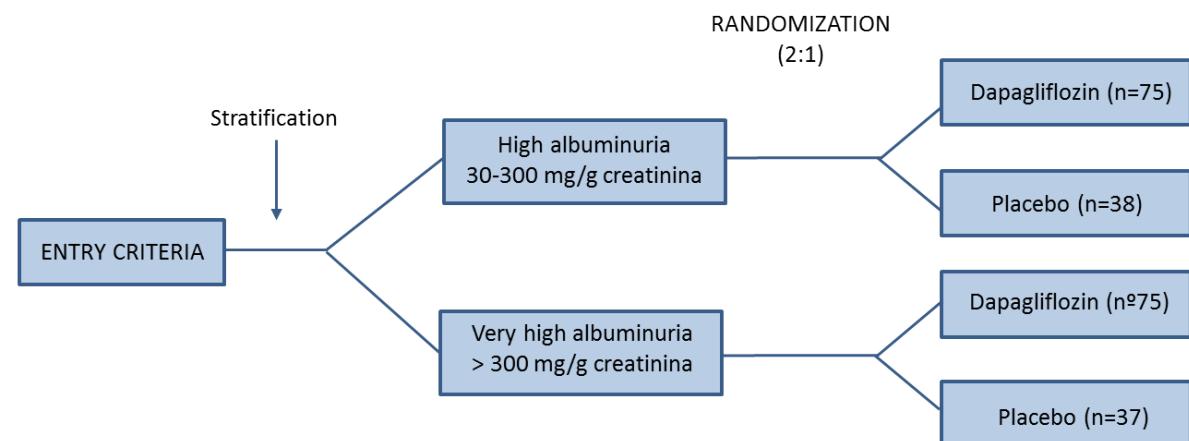
3.4. RANDOMIZATION

Two strata will be considered based on albuminuria levels:

- High albuminuria (30-300 mg/g creatinine)
- Very high (>300 mg/g creatinine)

Patients will be randomized to either dapagliflozin or placebo in a 2:1 ratio.

Figura 2.-Randomization scheme



Total number of patients: 225; distributed as:

- 150 diabetic patients treated with dapagliflozin (10mg/day in a single dose), half of them with high albuminuria levels (albuminuria 30-300 mg/g of creatinine) and half with very high albuminuria levels (albuminuria > 300 mg/g of creatinine)

- 75 diabetic patients treated with placebo, half of them with high albuminuria levels (albuminuria 30-300 mg/g of creatinine) and half with very high albuminuria levels (albuminuria > 300 mg/g of creatinine)

Randomization will be stratified by albuminuria strata and participating hospital (three hospitals); center specific randomization lists (active treatment or placebo) will be prepared centrally at the project office with a treatment code assigned to each patient.

Allocation will be concealed by means of sequentially numbered, opaque, sealed envelopes that contain the medication code assigned. The envelopes have to be opened sequentially and only after the participant's name is written on the appropriate envelope.

3.5. DRUG UNDER EVALUATION. BLINDING AND RELABELLING OF THE MEDICATION

The investigational medicinal product (IMP) is dapagliflozin 10 mg given once daily (film coated tablets, oral use).

The comparator will be placebo matching dapagliflozin 10 mg.

Either dapagliflozin or placebo will be administered through out the planned intervention period of the study (12 weeks).

AstraZeneca will donate both dapagliflozin 10 mg and placebo resembling dapagliflozin 10 mg for the study.

Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Dapagliflozin	10 mg, Green, plain, diamond shaped, film coated tablet (orally)	AstraZeneca
Matching placebo for dapagliflozin	Green, plain, diamond shaped, film coated tablet (orally). Does not contain active ingredient	AstraZeneca

Primary packaging of the Investigational Medicinal product (IMP) will be carried out by AstraZeneca or their designee in accordance with Good Manufacturing Practice (GMP).

Unlabeled bottles (identical) containing 35 tablets of each IMP will be provided by AstraZeneca.

The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals.

Label, storage and distribution are a promotor's responsibility.

Preparation and labelling of Investigational Medicinal Product

To allow for adequate treatment for the diabetes, only participants will be blinded to the treatment they receive. Attending physicians will know the group in which every patient is. To preserve blinding for the patient, the study medication (active and placebo) will be sent from AstraZeneca to a certified company (LogistaPharma), where, in coordination with the CRO of the study [ODDS, S.L.], it will be counted, labeled and distributed to the participating centers. The IMPs will be labelled in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines for labeling. The labels will fulfill GMP Annex 13 requirements for labelling.

LogistaPharma will send labeled medication with the corresponding randomization codified list to Hospital 12 de Octubre (Pharmacy Service). The investigator coordinator of the trial will distribute the medication **to** the primary care investigators. The study is single blinded, every investigator in each of the sites will have the randomization list with the individual treatment codes for each individual patient. The unblinding for the patient must not be done unless in medical emergencies. If the codes are broken for an individual patient, the promotor must be notified and decision if the data should be excluded from the analysis must be done by the promotor

The patient will receive the labelled medication, and counting of the pills will be done in the following visits: week 4, week 8 and week 12. Patients will also receive the medication leaflet of dapagliflozin, as stated in the form "Information for the patient"

Storage

All study drugs will be kept in a secure place under appropriate storage conditions. The IMP label on the bottle specifies the appropriate storage.

At the end of the study, all the study medication that has not been used will be collected from the patients by the investigators to be properly destroyed.

3.6. DRUGS NOT PERMITTED DURING THE CLINICAL TRIAL

While in the clinical trial, this protocol does not permit the use of the following drugs and/or changes in medication:

- Loop diuretics.
- SGLT2 inhibitors.
- Pioglitazone

If the attending physician considers that for the best care of the patient the use of any of the above mentioned drugs or changes in treatment is absolutely essential, the patient will be withdrawn from the study, the blinding for the patient will be broken and the promotor informed.

Any other change in medication which does not lead to withdrawal from the study will be recorded in the CRD.

3.7. INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The summary of the product characteristics details the interactions of dapagliflozin as follows:

Pharmacodynamic interactions

Diuretics

Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin.

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin

Interaction studies conducted in healthy subjects, using mainly a single dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin,

pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products

In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Other interactions

The effects of smoking, diet, herbal products and alcohol use on the pharmacokinetics of dapagliflozin have not been studied.

Paediatric population

Interaction studies have only been performed in adults.

Population of advanced age (65-75 years old)

Population older than 65 years of age are more likely to have a mildly reduced glomerular filtration rate (eGFR 60-90 mL/min $\times 1.73m^2$) and/or being on treatment with drugs that may affect renal function (as ACE inhibitors or Angiotensin-2 receptor blockers). In these patients, as in the usual clinical practice, administration of dapagliflozin should be done with extra caution (education of the patient and self monitoring of symptoms).

Specific drug alert

Severe cases of diabetic ketoacidosis associated with treatment with canagliflozin, dapagliflozin and empagliflozin have been reported. It is recommended to health professionals:

- Perform monitoring of ketone bodies in patients who develop symptoms suggestive of diabetic ketoacidosis during treatment even when blood glucose levels do not suggest diagnosis.
- Inform patients in treatment about the symptoms of diabetic ketoacidosis and the need to see the doctor if they occur.

3.8. END POINTS

Primary: Changes in mean nocturnal BP from baseline (week 0) to last visit (week 12).

Secondary:

- Changes in office BP from baseline (week 0) to last visit (week 12).
- Changes in HbA1C from baseline (week 0) to last visit (week 12).
- Changes in albuminuria from baseline (week 0) to last visit (week 12).
- Natural variability of mean nocturnal BP on separate visits (placebo group).

3.9. VISITS, VARIABLES AND MEASUREMENTS

Four clinical visits are planned in every patient at 0 (recruitment and randomization), 4, 8 and 12 weeks. Information on personal and family history of disease, clinical examination (including office BP determination), ABPM and blood and urine samples will be obtained on visits 0. The variables measured in the blood and urine samples depend on the criterium of the attending physician. For this trial, only HbA1c, serum creatinine, estimated glomerular filtration rate (eGFR) and albuminuria are mandatory. All this information, except personal and family history of disease, will also be collected at week 12 (see “3.20. Conduct of the study”). Thirty days after the end of the medication (visit of week 12) all participants will be contacted by telephone to assess safety. For the initial laboratory data required in the CRF, data obtained in primary care in the previous 3 months could be valid. These data will be repeated at the end of the study. Informed consents for the study will be signed by the patients before coming to the hospital. Blood samples extractions included in this protocol will be done, handled and analyzed at each clinical setting according to usual clinical

practice. No blood sample storage will be needed in this study. Extra blood samples drawn will be handled as described in “3.23. Addendum”.

The relationship of the procedures performed at every clinical visit is presented below (see “3.20. Conduct of the study”). Case report forms (CRFs) are presented in Annex I. Albuminuria will be measured according to generally used and previously described methodologies(18-23).

ABPM will be measured using Mobil-o-Graph that will give us 24 hours brachial and central BP as well as pulse wave velocity and heart rate(24). As diary of activity of the patient will not be recorded, in this study, nocturnal (or nighttime) blood pressure refers to measurements within the period from 12.00 p.m. to 6.00 a.m.

3.10. WITHDRAWAL OF PATIENTS FROM THE STUDY AND UNBLINDING

Any patient can be withdrawn from the study at anytime during follow-up based on medical criteria of attending physician. The latter will detail the reasons of the withdrawal and communicate it urgently to the coordinating office of the trial if needed. If the reason for withdrawal is an adverse event (AE), the patient will be followed according to the procedures described for AEs (3.16).

Any patient can decide to abandon the study at any time during the study.

Withdrawal from the trial for any reason is definitive. When leaving the study, the main reason will be recorded and, if possible, the patient should have a final exam with the content of the visit of week 12. Patients that abandon the study will not be substituted.

All the above mentioned situations cause unblinding of the study. The primary care physician is always aware of the medication that receives the patient (single blind) and

will be the contact person and responsible to break the blind. Contact details are available in the patient information form. After unblinding, the responsible primary care physician will report it to the coordinating office of the project (ODDS, S.L., proyectos@odds.es).

3.11. SAMPLE SIZE CONSIDERATIONS

For the main objective of the study, changes in mean nocturnal systolic blood pressure will be compared between the active treatment and placebo groups.

The use of SGLT2 inhibitors has been reported to be associated with reductions in office blood pressure of 4–8 mmHg, reductions that could be even higher with the use of ambulatory BP monitoring.¹⁵

Accepting an alpha error of 0.05 in a two-sided test, 150 patients are needed in the active treatment group and 75 in the placebo group (2:1 randomization) to have an 80% power (beta error=0.2) to detect as statistically significant a difference greater than or equal to 5 mmHg in mean nocturnal BP between placebo and active treatment (conservative estimate of the expected effect). The standard deviation is assumed to be 12 mmHg and it is expected a drop-out rate of 9%.

In the prespecified subgroup analysis by albuminuria levels, this sample size (75 in active treatment and 37 in placebo) allows to detect as statistically significant, within each albuminuria stratum and with the same assumptions and alfa and beta errors, a difference greater than or equal to 7,1 mmHg in the reduction of mean nocturnal BP between both groups (active treatment and placebo), an effect still within what can be expected.

3.12. DATA MANAGEMENT

Data will be collected in an electronic CRF by participating doctors and nurses both at the hypertension units and at primary care centers. A range of acceptable values and logical rules among variables will be implemented to improve quality of data and reduce the need of queries.

The processing, communication and transfer of data will be in accordance with the provisions of the Organic Law 15/1999, December 13th, on the protection of personal data.

Trial documentation will be kept and storaged in each site for 25 years after completion of the study.

3.13. PLAN OF ANALYSIS

The main analysis will compare baseline and final visit values of nocturnal blood pressure and all the rest of quantitative variables of interest within each stratum of albuminuria by means of paired t-test. Changes of nighttime blood pressure from baseline to final visit among patients with high and very high albuminuria levels will be compared to placebo with t-test.

Variables will be described by means of mean (and standard deviation) or proportion depending on the type of variable considered. Whenever the test of hypothesis may involve discrete variables, chi-squared test will be used.

Comparability of treatment and placebo groups will be tested (t-student or chi-squared test, depending on the variable) to assess randomization, and linear regression will be used to adjust for potential confounders, if needed; stratum of albuminuria at randomization will be forced in the model.

To respond to secondary objectives, the same analyses will be done for each stratum of albuminuria at randomization.

Only patients that complete the 3-month follow-up will be analyzed. Patients who do not complete the follow-up will be compared to those who adhere to the protocol.

No interim analysis is planned. A *p* value<0.05 will be considered as statistically significant.

3.14. END OF THE TRIAL

The trial will end with the last visit of the last patient recruited. Details of the planned chronogram can be seen in 3.21

As no interim analysis are planned (see 3.13), no formal stopping rules of the trial are considered in this regard.

The study may be terminated if the study procedures are not being performed according to Good Clinical Practice (GCP). The promotor also may terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin.

3.15. ETHICAL ISSUES

At the recruitment visit, all patients meeting criteria and invited to participate will receive adequate written information on the study (Annex II) and will have the opportunity to ask the investigator any question regarding their participation and will be given enough time to make a decision. Following all this, they will sign and date their acceptance to participate in it (Annex III) prior to randomization. This is a trial

proposed as “low level of intervention trial” [“RD 1090/2015 de 4 de diciembre”] and every participant will be covered by an insurance for this instances.

This study will be done conforming to the principles of the Declaration of Helsinki and posterior amendments, Good Clinical Practice and the applicable legislation including the requirements of the Spanish law of data protection (“Reglamento General de Protección de Datos (Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016”, “Ley Orgánica 15/1999 de 13 de diciembre, de protección de datos de carácter personal”, and “RD1720/2007”), as described in the “Information for the patient sheet” (Annex II). Data will be entered online and stored securely in a centralized database in a devoted server. To access the eCRF, an user name and password with limited access to allow the development of the study will be assigned to every investigator in the trial (including coordinators and CRO). All personal identification data of the patients will be dissociated from the rest of the data and only the attending physicians will have access to that information to allow the follow-up. All data will be treated anonymously in the analysis and no report from the study will contain any information that allows to identify the patients.

The clinical study will be reviewed by health authorities and an ethic committee and the study will only be started when the approval from the regulatory authorities and the ethic committee is obtained.

At the end of follow-up, every patient will be informed of the treatment group in which he remained during the study and continue the standard care for his/her condition by his/her attending physician.

3.16. POTENTIAL RISKS AND BENEFITS OF THE STUDY

The drug under investigation is accepted and of common use in Spain for the treatment of the type of patients that will be included. It will be administered as approved in its specifications. Its use is evidence based and its safety and efficacy are well documented.

All tests and procedures included in the study are normal clinical practice in the diabetic patient with the exception of ABPM that poses no risk for the patient and is basic for the main outcome of the study.

3.17. QUALITY CONTROL

Filters and logic rules will be implemented in the electronic CRF to minimize data entry errors. Throughout the study, 10% of the clinical sites will be randomly selected and visited by CRO (ODDS, S.L.) staff to monitor quality of data.

3.18. SAFETY AND MONITORING OF ADVERSE REACTIONS

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

Adverse events will be monitored and registered during the study and communicated both to the promotor and to the “Agencia Española de Medicamentos y Productos Sanitarios” as by law (RD 1090/2015, December 4th).

3.18.1. Definition of adverse event

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a

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

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

3.18.2. Definitions of serious adverse event

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

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

3.18.3. Definition of suspected unexpected serious adverse reaction (SUSAR)

As described in “REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC” the following definitions on suspected

unexpected serious adverse reaction (SUSAR) will apply in this protocol: A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

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

3.18.4 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period up to and including the 30-day follow-up period. All ongoing and any new AEs/SAEs identified during the 30 calendar days follow-up period after the last dose of study medication must be followed to resolution. After study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in study patients. If an Investigator learns of any SAEs, including death, at any time after a patient has completed 30 days post treatment follow-up period, and he/she considers there is a reasonable possibility that the event is causally related to the study treatment, the investigator should notify the promotor by reporting the SAE.

Follow-up of unresolved adverse events

Any SAE or non-serious adverse event that is still ongoing during the 30-day follow-up visit must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. AstraZeneca may request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if necessary.

The following variables will be collected for each AE:

- AE (verbatim).
- The date when the AE started and stopped.
- Whether the AE is serious or not.
- Investigator causality rating against the Investigational Product (yes or no).
- Action taken with regard to investigational product.
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE.
- Date Investigator became aware of serious AE.
- AE is serious due to.
- Date of hospitalization.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Description of AE.
- Causality assessment in relation to Study procedure(s).
- Causality assessment in relation to Other medication.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 3.18.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the

other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

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

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

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

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

Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported

Reporting of serious adverse events

The investigator will report immediately (first 24 h) any SAE by means of filling and sending the corresponding form [Annex IX] to the CRO (ODDS, S.L.) by fax [981 217539] or e-mail [proyectos@odds.es].

The promotor/CRO must inform the AEMPS of any Suspected unexpected serious adverse events (SUSAR) that occur in accordance with the reporting obligations, and will concurrently forward all such reports to AZ. A copy of the report must be sent by e-mail to AstraZeneca at the time the event is reported to the AEMPS. It is the responsibility of the promotor to compile all necessary information and ensure that the AEMPS receives a report according to the AEMPS reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

* A **cover page** should accompany the **SAE** form indicating the following:

- External Scientific Research (ESR)
- The investigator's name and address
- The trial name/title and AstraZeneca ESR reference number

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

* ***SAE report and accompanying cover pagewill be sentby way of Email to AEMailboxClinicalTrialTCS@astrazeneca.com.***

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the AEMPS.

Serious adverse events that do not require expedited reporting to the AEMPS need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported under no circumstance less frequently than quarterly.

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

3.19. PUBLICATION POLICY

The investigators will submit the main results of the study to be published in a journal related to the topic of the trial.

3.20. CONDUCT OF THE STUDY

The table below shows the plan of visits for every patient participating in the study and

the procedures to be done at every visit and where it takes place.

	Visit 0 (recruitment&randomization)		Visit Week 4 (±3 days)	Visit Week 8 (±3 days)	Visit Week 12 (final visit)	Phone Call (30 days after the final visit)
	Primary care	Hospital (within 7 days from primary care visit)	Primary care	Primary care	Hospital	Hospital
Verification of inclusion and exclusion criteria and obtention of informed consent	✓					
Randomization and drug distribution for the entire follow-up		✓				
Personal and family history	✓					
Office BP	✓		✓	✓	✓	
Pill counting			✓	✓	✓	
Clinical exam	✓		✓	✓	✓	
Blood sample (to confirm entry criteria; recent [previous three months] analyses are acceptable) and urine	✓	✓ ^(*)			✓	
ABPM		✓			✓	
Adverse events monitoring			✓	✓	✓	✓

(*)

Only necessary if not all measurements in the blood sample drawn in primary are available

3.21. PLANNED CHRONOGRAM OF THE STUDY

Administrative issues: 3 months (September-November 2018)

AEMPS/Ethical committee approval to first subject in: 1 month

First subject in: December 2018

50% enrollment: April 2019

Last subject in: June 2019

Last subject last visit: September 2019

Recruitment of patients: 7 months (December 2018-June 2019)

Data cleaning and closing of the database: 3 months (October 2019-December 2019)

Data analysis: 4 months (January 2020- April 2020)

Final report and drafting of the manuscript: May 2020

3.22. BUDGET

Astra-Zeneca will provide funding for the study.

3.23. ADDENDUM

Patients included in this study will be part of an ongoing project financed for the period 2018-2020 by the “Fondo de Investigaciones Sanitarias (Instituto de Salud Carlos III), Referencia: PI17/01193” approved by the ethics committee of Hospital 12 de Octubre with the title “Papel de la presión arterial nocturna en la estratificación del riesgo cardiovascular: nuevas estrategias clínicas y experimentales” and aimed to evaluate oxidative stress, vascular remodeling and proteomic profiles in different clinical situations. To this end, coinciding with the blood extractions done in the hospital in this protocol (visits 0 and week-12), extra blood samples will be obtained, prepared and stored. Four blood tubes (7 ml/each) will be drawn, centrifuged and the plasma separated and stored in a private collection at Hospital 12 de Octubre (Dr. Ruiz Hurtado). This information is included in the information for the patient sheet.

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