CLINICAL TRIAL PROTOCOL

Protocol Signature Page

STUDY TITLE:

COMPARATIVE EFFECTS OF MOXONIDINE AND BISOPROLOL ON BONE METABOLISM, VASCULAR AND CELLULAR MARKERS OF AGING, BLOOD PRESSURE IN HYPERTENSIVE POSTMENOPAUSAL WOMEN (COMPASS)

Protocol No.	MOXOC001
Version	Version 1.0
Date of the protocol final version:	19/11/2014
Study Sponsor:	Autonomous Nonprofit Organization "Society of experts in innovative technologies in medicine" (ANO "OSO ITEM")
Protocol author:	Olga Nikolaevna Tkacheva, MD, PhD, professor

19.11.2014

Signature Data

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PROJECT SYNOPSIS

Study Title	Comparative effects of moxonidine and bisoprolol on bone metabolism, vascular and cellular markers of aging, blood pressure in hypertensive postmenopausal women
Study Sponsor:	Autonomous Nonprofit Organization "Society of experts in innovative technologies in medicine" (ANO “OSO ITEM”)
Principal Investigator	O.N. Tkacheva, MD, PhD, professor
Therapeutic area / indication	Cardiology, essential hypertension
Study objectives and goals	**Primary Objective:** To investigate the effect of moxonidine versus bisoprolol on collagen type 1 C-telopeptide in postmenopausal female patients with arterial hypertension and osteopenia. **Secondary Objectives:** 1. To investigate the effect of moxonidine versus bisoprolol on bone metabolism and bone tissue density in postmenopausal female patients with essential hypertension and osteopenia. 2. To investigate the effect of moxonidine versus bisoprolol on the processes of cellular and vascular aging in postmenopausal female patients with essential hypertension and osteopenia. 3. To investigate efficacy of antihypertensive therapy with moxonidine versus bisoprolol in hypertensive postmenopausal women.
Study Design	Randomized, open-label, interventional, comparative clinical trial Study population is postmenopausal women with essential hypertension and osteopenia. The study will enroll 114 patients after screening (it is expected that 300 patients will need to be screened to reach this enrolrollment goal). After the informed consent signing, the patient's participation in the study will include the period before the studied product administration, treatment period and a final visit. Patients will be randomized to one of two groups: moxonidine group or bisoprolol group. According to the study protocol, patients randomization to the control and investigated groups will be carried out using a simple envelopes method and, therefore, it is assumed that the control and the main groups will be matched by the basic measured parameters; the number of subjects in the main and control groups is planned to be equal. The study endpoints are measured prior to the studied product initiation (V1) and after completion of 48-week treatment with the investigated product (V4).

	The period prior to the studied treatment initiation is designed to assess the patient meeting inclusion criteria and to carry out 7-10-day washout period in patients with previous antihypertensive therapy. The planned duration of the period before the treatment initiation does not exceed 14 days after the signing of the informed consent form by the patient. Then, at the enrollment visit during the treatment period, the investigator will assess the patient meeting the inclusion criteria. If the inclusion criteria are met, the patient will be enrolled in the study. The baseline condition data will be obtained from the patient, then the patient will be randomized to one of the two treatment groups (moxonidine or bisoprolol). The treatment period involves the enrollment visit (V1), and 3 more visits. The final visit 4 is carried out at week 48 after the enrollment visit, the patient then completes the study. The patients' treatment includes gradual titration of the studied products doses. Group 1 will receive moxonidine with the dose titrated to a maximum, and then, if necessary, the patient will be shifted to the combination therapy (Step 2 – adding an ACE inhibitor) Group 2 will receive bisoprolol with the dose titrated to a maximum, and then, if necessary, the patient will be shifted to the combination therapy (Step 2 – adding an ACE inhibitor). After randomization to moxonidine and bisoprolol groups (V1), patients start treatment with 0.4 mg moxonidine QD or 5 mg bisoprolol QD. If the target BP (<140/90 mmHg) is reached in 2 weeks, the patient continues taking the medication at the same dose. If the target BP is not reached in 2 weeks, the moxonidine dose is increased to 0.6 mg QD, the dose of bisoprolol is increased to 7.5 mg QD. If the target BP is not reached in 2 weeks of treatment with the increased doses, an ACE inhibitor (perindopril) at a dose of 10 mg/day is added at the 8th week of the study. In case of intolerance to perindopril, losartan at a dose of 50 mg/day will be administered. During the study, the patient will have parameters of efficacy, tolerability and safety of the therapy with moxonidine or bisoprolol regularly assessed.
Study Groups	**Investigated group**: postmenopausal women with essential hypertension and osteopenia treated with moxonidine. **Comparative group**: postmenopausal women with essential hypertension and osteopenia treated with bisoprolol.
Randomization procedure	Simple randomization using the method of envelopes
Number or patients	114 patients.
Screening inclusion criteria	1. Female with age 45 years and older. 2. Postmenopausal (absence of menstrual periods for a minimum of 12 months) at the moment of Informed Consent sign. 3. Arterial hypertension grade I / II per ESH/ESC 2013

	guidelines (diastolic pressure ≥ 90 and <110 mm Hg, systolic pressure ≥140 and <180 mm Hg). 4. Not achieving BP targets <140/90 mmHg either during antihypertensive therapy or naive. 5. Absence of moxonidine or bisoprolol treatment at least 6 months before the study 6. Osteopenia of lumbar spine and/or proximal part of the femur (osteoporosis T-score from -1 to -2.5 standard deviations [SD]) by X-Ray densitometry. 7. Signed Informed Consent for participation in the study.
Screening exclusion criteria	1. Hypersensitivity to moxonidine, bisoprolol or any other ingredient of the respective formulations 2. Any Contraindications for moxonidine, bisoprolol 3. Osteoporosis (T-score below - 2.5 SD). 4. Primary or secondary hyperparathyroidism. 5. Paget's disease of bones. 6. History of low traumatic bone fractures. 7. Malabsorption syndrome. 8. History of gastro-intestinal surgery. 9. Severe disturbance of peripheral circulation. 10. Raynaud's disease. 11. Symptomatic (secondary) hypertension (caused by any primary internal diseases) 12. Morbid obesity (BMI over 40 kg/m2). 13. Symptoms of estrogen deficiency such as hot flushes, nights sweat, vaginal dryness 14. Administration of any hormone-replacement therapy (HRT) or intake of isoflavones 15. Secondary hypogonadism. 16. SistBP ≥180 mm Hg and/or DiastBP ≥110 mm Hg. 17. Clinical presentations of cardiovascular disease: coronary heart disease (CHD), history of stroke, transient ischemic attack (TIA), Charcot's syndrome. 18. Severe heart failure. 19. Hemodynamically significant congenital heart disease. 20. Heart rhythm disorders which require permanent use of any antiarrhythmic medications (including β-adrenoblockers and calcium antagonists). 21. Diabetes mellitus of any genesis. 22. Severe liver failure. 23. Severe kidney failure including patients on dialysis 24. Thyroid diseases accompanied by functional disorders (thyrotoxicosis or uncompensated hypothyroidism). 25. Alcohol and drug abuse. 26. Patients with oncological diseases diagnosed within 5 years before IC execution. 27. Inability of the patient to comprehend the essence of the program and to provide his/her consent for participation

	in the program. 28. Patients with any condition, which in the opinion of the Investigator makes the patient unsuitable for inclusion based on clinical judgment. 29. Corticosteroid therapy 30. Participation in any other clinical study during the whole course of this investigation including participation in a study within 30 days prior to providing the informed consent for this trial
Start of treatment criteria	1) Patient is to meet all the inclusion criteria and should lack any of the exclusion criteria. 2) Patients previously treated with antihypertensive agents have undergone 7-10-day washout period according to the protocol (all antihypertensive drugs are discontinued, except fast-acting agents to relieve hypertensive episodes).
Duration of the study	Patients' enrollment – 12 months. The total duration of the study is 48-50 weeks. (Screening period (1-14 days) and washout period (7-10 days), every patient will be treated for up to 48 weeks). FPFV – Q1.2015 LPFV – Q1.2016 LPLV – Q1.2017 CSR – Q3.2017
Investigated product. **Dose, method of administration**	Film-coated tablets of Moxonidine (Physiotens) manufactured by Rottendorf Pharma GmbH, Germany, packaged and released by Abbott Healthcare SAS, France. One tablet contains 0.40 mg moxonidine as an active substance and the following excipients: lactose monohydrate - 95.60 mg; povidone K25 - 0.70 mg; crospovidone – 3.00 mg; magnesium stearate - 0.30 mg; hypromellose 6mPas - 1.300 mg; ethyl cellulose aqueous Disp.30% - 4.000 mg (solids 1.200 mg) ; macrogol 6000 - 0.250 mg; talc - 0.875 mg; red ferric oxide (E172) - 0.125 mg; titanium dioxide (E171) - 1.250 mg. There are 14 tablets in the blister; the carton contains 1, 2 or 7 blisters. One tablet contains 0.20 mg moxonidine as an active substance and the following excipients: lactose monohydrate - 95.80 mg; povidone K25 - 0.70 mg; crospovidone – 3.00 mg; magnesium stearate - 0.30 mg; hypromellose 6mPas - 1.300 mg; ethyl cellulose aqueous Disp.30%- 4.000 mg (solids 1.200 mg); macrogol 6000 - 0.250 mg; talc - 0.9975 mg; red ferric oxide (E172) - 0.0025 mg; titanium dioxide (E171) - 1.250 mg. There are 14 tablets in the blister; the carton contains 1, 2 or 7 blisters.

	Moxonidine is taken orally, once or twice a day, regardless of meals. Maximum daily dose of moxonidine is 0.6 mg. Duration of treatment: Moxonidine 0.4 mg is prescribed to postmenopausal patients with hypertension and osteopenia once or twice a day. Subsequently, in patients with no response, the daily dose is titrated up to 0.6 mg QD; then perindopril 10 mg may be added to the regimen at week 8, if necessary. In case of intolerance to perindopril, losartan at a dose of 50 mg/day will be administered.
Comparative product. **Dose, method of administration**	Bisoprolol, film-coated tablets One tablet contains bisoprolol hemifumarate and bisoprolol fumarate (2: 1) as active substances 5 mg, and the following excipients: calcium hydrogen phosphate anhydrous - 132 mg; corn starch fine powder - 14.5 mg; colloidal anhydrous silica - 1.5 mg; MCC - 10 mg; crospovidone - 5.5 mg; magnesium stearate - 1.5 mg film coating: hypromellose 2910/15 - 2.2 mg; macrogol 400 - 0.53 mg; dimethicone 100 - 0.11 mg; iron oxide yellow dye (E172) - 0.02 mg; titanium dioxide (E171) - 0.97 mg. Bisoprolol is taken orally, once a day, regardless of meals. Bisoprolol 5 mg is prescribed to postmenopausal patients with hypertension and osteopenia. Subsequently, in patients with no response, the daily dose is titrated up to 7.5 mg every 2 weeks; then perindopril 10 mg may be added to the regimen at week 8, if necessary. In case of intolerance to perindopril, losartan at a dose of 50 mg/day will be administered.
Other agents allowed by the protocol	Losartan film-coated tablets produced by Berlin-Chemie, Germany. Each tablet contains 50 mg of losartan. Losartan is taken orally, once a day, regardless of meals. The product is prescribed to postmenopausal patients with hypertension and osteopenia non-responsive to moxonidine or bisoprolol monotherapy for 4 weeks and intolerant to perindopril. Calcium carbonate + cholecalciferol, chewable tablets Each tablet contains the following active ingredients calcium carbonate 1250 mg (equivalent to 500 mg of elemental calcium), cholecalciferol (vitamin D_3) 5 mcg (200 IU) (as cholecalciferol concentrate - 2 mg). excipients: sorbitol - 390 mg; isomalt - 62 mg; povidone - 36.4 mg; magnesium stearate - 6 mg; aspartame - 1 mg; orange oil - 0.97 mg; mono- and diacylglycerols - 0.0008 mg. The product is taken orally during meals, it should be chewed or dissolve in the mouth.

Endpoints	**Primary endpoint**: Changes in mean values of the bone resorption marker (collagen type 1 C-telopeptide) at the end of the study (V4) from the baseline (V1) in comparison between the groups. **Secondary endpoints**: 1) To assess mean values of osteocalcin at visit 4 versus baseline level (visit 1) and comparison between the groups 2) To assess mean values of the receptor activator of nuclear factor kappa-B ligand (RANKL) at visit 4 versus baseline level (visit 1) and comparison between the groups 3) To assess mean values of BMD at visit 4 versus baseline level (visit 1) using control dual-energy X-ray absorptiometry and comparison between the groups 4) To assess mean telomerase activity at visit 4 versus baseline level (visit 1) and comparison between the groups 5) To assess mean pulse wave velocity (PWV) at visit 4 versus baseline level (visit 1) and comparison between the groups 6) To assess mean intima-media thickness (IMT) at visit 4 versus baseline level (visit 1) and comparison between the groups 7) To estimate the proportion (%) of patients who achieved target blood pressure <140/90 mmHg at the visit 2 (week 8), visit 3 (week 24) and 4 (Week 48) and according to the patient's diary.
Evaluation of pharmacokinetic / pharmacodynamic parameters	The parameters will not be evaluated
Evaluation of quality of life / pharmacoeconomic parameters	The parameters will not be evaluated
Statistical Analysis	**Efficacy Analysis**: Changes in mean values of the bone resorption marker (collagen type 1 C-telopeptide) at the end of the study (V4) from the baseline (V1) are evaluated in comparison between the groups. Changes in mean values of the receptor activator of nuclear factor kappa-B ligand (RANKL) at visit 4 versus baseline level (visit 1) in comparison between the groups. Changes in mean values of BMD at visit 4 versus baseline level (visit 1) using control dual-energy X-ray absorptiometry and in comparison between the groups.

	Changes in mean telomerase activity at visit 4 versus baseline level (visit 1 in comparison between the groups. Changes in mean pulse wave velocity (PWV) at visit 4 versus baseline level (visit 1) and in comparison between the groups. Changes in mean intima-media thickness (IMT) at visit 4 in comparison between the groups. The efficacy of the investigated treatment is estimated based on whether target blood pressure (<140/90 mm Hg) at visits V2, V3 and V4 is reached. **Safety Analysis**: Adverse events (AEs) are recorded at every visit. Analysis of adverse events and serious adverse events is conducted to determine the total number of AEs, the total number of patients with adverse events, the number of treatment-related adverse events, the number of AEs associated with product discontinuation and the number of voluntary withdrawal of informed consent. Rate and severity of all adverse events and drug-related adverse events (i.e., at least "possibly" associated with the studied product) will be summarized by organ systems. Data on the product withdrawal due to adverse events will be summarized in tables. **Statistical methods:** Statistical analysis will be conducted under the supervision of a responsible biostatistician. The details of statistical analysis will be provided in the statistical analysis plan in accordance with the GCP requirements and other relevant requirements and laws. The statistical analysis plan will be finalized before the data lock point. All deviations from the final statistical plan version will be justified in the final program report. The results will be combined for the complete study sample. Two-sided levels of significance and confidence intervals will be calculated. The significance of differences will be calculated for two-sided tests, with a critical significance level of 0.05. For parameters of interval scale type, the following will be calculated: the arithmetic mean (95% confidence interval for the mean), standard deviation, median, 25th and 75th percentiles. For parameters of ordinal scale type, median, 25th and 75th percentiles will be calculated. For parameters of nominal scale type, frequency categories and confidence intervals for the frequencies (modified Wald method) will be calculated. If the assumptions made during the preliminary study planning are found to be erroneous, the analysis methods will be modified to conduct a more suitable analysis. The result of the primary endpoint analysis will be presented as an absolute number and

	proportion (%) of patients with target BP (<140/90 mm Hg) achieved at visit V4. Statistical analysis will be carried out using SPSS / PASW Statistics software package (version 18), SPSS Inc., Chicago, Illinois, USA. **Rationale for sample size** As this is an explorative study with open design no formal sample size calculation was performed. The focus of the study is to obtain scientific data for a publication and taking into account a reason of feasibility of enrollment to timelines and screening of 300 patients per year in assumption that ratio of screened / enrolled patients is approximately 3 to 1 so it is expected that not less than 100 patients but no more than 114 patients will be enrolled in the study. According to this approach the total sample size is chosen 114 subjects.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACEI - angiotensin-converting enzyme inhibitor

AE - adverse event

ALT - alanine aminotransferase

AR - adverse reaction

AST - aspartate aminotransferase

BB - beta-blockers

BMD - bone mass density

BMD - bone mineral density

BP - blood pressure

CHD - coronary heart disease

CRF - case report form

CTX - collagen type 1 C-telopeptide

CVD - cardiovascular disease

DBP - diastolic blood pressure

ECG - electrocardiogram

HCF - health care facility

HR - heart rate

HTN - hypertension

IMT - intima-media thickness

OC - osteocalcin

OPG - osteoprotegerin

PWV - pulse wave velocity

RANKL - Receptor activator of nuclear factor kappa-B ligand

SAE - serious adverse event

SBP - systolic blood pressure

TIA - transient ischemic attack

Site conducting the study – Federal State-Funded Institution "State Scientific Research Center of Prophylactic Medicine" of the Ministry of Healthcare of Russian Federation (FSFI "SSRCPM" of the Ministry of Healthcare of Russia)

Principal Investigator – O.N. Tkacheva, MD, PhD, professor

1. INTRODUCTION

1.1 Rationale

It is known that cardiovascular disease (CVD) associated with atherosclerosis is the major cause of morbidity, disability and mortality in developed countries and, according to WHO estimates, in the next decade, CVD may become the leading cause of death in developing countries as well [1]. At the same time, the CVD epidemic is unfolding in the setting of significant advances in the diagnosis and treatment of these conditions. One reason for such a dramatic increase in heart attack, stroke, and heart failure incidence is thought to be the steadily aging population. It is due to the fact that age-related changes of blood vessels are an important risk factor for CVD. Growing evidence has been accumulated that aging-related changes in the vascular wall produce metabolically and enzymatically active environment that promotes initiation and progression of vascular disease. The more pronounced the age-related vascular wall changes are, the easier and faster atherosclerosis, hypertension and other CV disorders develop, which, in turn, accelerates the age-related changes.

The main signs of vascular aging include arterial wall thickening, subclinical atherosclerosis, vascular calcification and increased arterial stiffness, of which the increased vascular stiffness is a key sign of vascular aging [2, 3]. It is known that aside from hypertension, the chronic indolent inflammation associated insulin resistance plays a fundamental role in the increase of vascular wall stiffness [4]. In recent years, more data have been accumulated on the role of cellular senescence in the development of vascular aging. One of the major theories of cellular senescence is based on the telomere shortening. A telomere is a region of repetitive nucleotide sequences (TTAGGG) at the end of a linear chromosomal DNA. The main mechanism for maintaining telomere length is the restoration of telomere repetitive DNA sequences by the enzyme telomerase. The assessment of telomerase enzyme activity in combination with other parameters enables to evaluate the rate of aging [5, 6]. Accelerated

telomere shortening and reduced telomerase activity may be due to oxidative stress, chronic inflammation and their associated processes, e.g., insulin resistance [7, 8].

It is believed that vascular and cellular markers of aging may be a useful additional criterion for evaluation of long-term effectiveness of therapy for chronic non-infectious diseases, e.g., arterial hypertension.

The postmenopause is a period in a woman's life that is characterized by accelerated aging processes, higher risk of hypertension and progressive insulin resistance.

There is no doubt that the search for effective targeted therapy of the main chronic non-infectious diseases aimed at not only treatment of the disease but also at slowing of the aging itself is a very promising research area.

Earlier clinical trials revealed a positive effect of moxonidine on insulin resistance suggesting that the drug may be a promising antihypertensive agent with a potential effect on cellular and vascular aging [9].

Other antihypertensive drugs have a short-term effect on the functional state of the arterial wall (owing to smooth muscle relaxation) and a long-term effect on its structure (primarily due to quantitative and qualitative changes in elastin and collagen). A meta-analysis based on the results of 15 randomized clinical studies has demonstrated that the arterial stiffness may be reduced in patients administered with antihypertensive medications regardless of the intensity of the antihypertensive effect [10].

Reduction of arterial stiffness in hypertensive patients was noted for ACE inhibitors, beta blockers (BB), angiotensin II receptor blockers, and calcium antagonists [11].

Along with hypertension, **osteoporosis** is one of the most pressing problems of women's health. Among all known forms of osteoporosis, the postmenopausal osteoporosis accounts for 85% of all osteoporosis cases. As we age, the bone metabolism is shifted towards bone resorption that leads to osteopenia, and to osteoporosis in subjects predisposed to rapid loss of the bone mass [12]. Bone strength depends on the amount of bone mass and quality of the bone tissue. Bone mineral density (BMD) is the measure of bone mass, while the bone tissue quality is characterized by bone turnover that is evaluated with biochemical markers of bone formation (e.g., osteocalcin, OC) and bone resorption (e.g., collagen type 1 C-telopeptide, CTx).

Several experimental studies have demonstrated that moxonidine may lower the activity of Na^+- independent Cl^-/bicarbonate exchanger (anion exchanger, AE) which plays an essential role in viability of osteoclasts that are crucial for bone resorption. The suppression of AE proteins activity has been proven to inhibit osteoclast activity and reduce bone resorption whereas the moxonidine molecule is known to reduce the AE protein activity. Therefore, the results of experimental studies have shown the ability of moxonidine to inhibit bone resorption through its effect on the osteoclast activity. Furthermore, the experimental studies demonstrated the ability of moxonidine to slow down the loss of the bone mass in laboratory animals which lays a foundation for clinical investigation of moxonidine effects on bone tissue density [9].

The discovery of the signaling system that includes receptor activator of nuclear factor κβ (RANK), its ligand (RANKL) and osteoprotegerin (OPG) acting as a main regulator of differentiation, functioning and apoptosis of osteoclasts, has made a breakthrough in the understanding of pathophysiology of osteoporosis. RANKL is produced by cells of osteoblast lineage, bone marrow stromal cells, synovial cells and activated T-cells. RANKL binds to OPG and plays the coordinating role in osteoclastogenesis, osteoclasts differentiation, activation and apoptosis. RANKL activation is an important preliminary step in osteoclast production and occurs with RANKL binding to pre-osteoclasts. OPG is a natural decoy receptor for RANKL and competes with RANK for binding RANKL. By blocking such binding, OPG suppresses bone resorption in favor of bone formation. The abnormal binding of RANKL to OPG is an essential link in the pathogenesis of many diseases associated with increased production of RANKL and increased bone resorption [13].

Vascular wall calcification is the most important aspect of the age-related changes. A number of studies have established that there is a clear inverse correlation between the degree of vessels calcification and the level of bone mineralization. This phenomenon was called the calcification paradox. Once the key proteins that stimulate or inhibit the extraskeletal calcification have been discovered, it has become clear that the vascular calcification is not only a passive process of calcium and phosphorus deposition but also an active process that involves vascular “ossification”. Numerous authors have confirmed the association between osteoporosis and vascular calcification in a general population [14].

Of all the components that most clearly indicate the link between bones and arterial wall, OPG attracts major attention. OPG is a part of a system whereby the osteoblasts modulate the osteoclastogenesis.

Increased OPG levels have been found in postmenopausal women with osteoporosis versus healthy women of corresponding age. It is suggested that the increased OPG level is a compensatory reaction to the increased osteoclast-mediated bone resorption. Normally, RANKL is not expressed in the vessels, however, its expression was found in OPG-deficient mice and in aortic valves of patients with calcified aortic valve stenosis. The elevated RANKL may be a link between bone tissue and vascular calcification [15].

All the above data suggest that the broadening of knowledge about OPG effects on the arterial wall and bones allows us to understand clinical and therapeutic value of OPG in osteoporosis and vascular calcification.

Published data contain information on positive effects of beta-blockers on the bone tissue condition. There are data which clearly demonstrate a positive effect of beta-blockers on bone mass. Thus, Australian researchers in a large-scale 20-year-long study involving 3488 patients have shown that a regular intake of beta blockers (BB) can increase bone mineral density (BMD) and prevent osteoporosis in 50% of patients [16].

In the population-based study of women older than 50 years (Geelong Osteoporosis Study), the association between beta blockers treatment and bone mineral density (BMD) or bone fractures has been estimated. The results have confirmed the association between the treatment with beta blockers and high level of BMD or low risk of bone fractures [16].

However, there are other studies that failed to confirm a positive effect on beta blockers on BMD (Study of Osteoporosis Fractures, Danish Osteoporosis Prevention Study, EPIDOS, Rotterdam Study). These studies pursued other goals and the effects of beta blockers on BMD were analyzed retrospectively. The analysis of the beta blockers efficacy was also complicated by the fact that the investigated group and the comparative group of patients differed from each other greatly in confounding factors that may have affected the amount and quality of the bone tissue (body mass, hormonal replacement therapy, smoking, statins and glucocorticoids treatment, etc.). Thus, there is currently no sufficient clinical experience to draw definitive conclusions about effects of beta blockers on BMD.

The proposed trial is a comprehensive study of moxonidine effects on processes of cellular and vascular aging as well as bone metabolism. We may not rule out a possible role of moxonidine in formation of calcification paradox.

2. PROGRAM OBJECTIVES

2.1 Primary objective: To investigate the effect of moxonidine versus bisoprolol on collagen type 1 C-telopeptide in postmenopausal female patients with arterial hypertension and osteopenia.

2.2 Secondary (experimental) objectives:

To investigate the effect of moxonidine versus bisoprolol on bone metabolism and bone tissue density in postmenopausal female patients with essential hypertension and osteopenia.

To investigate the effect of moxonidine versus bisoprolol on the processes of cellular and vascular aging in postmenopausal female patients with essential hypertension and osteopenia.

To investigate efficacy of antihypertensive therapy with moxonidine versus bisoprolol in hypertensive postmenopausal women.

3. PROGRAM PLAN AND PROCEDURES

3.1 General design

This is explorative, randomized, open-label, interventional, comparative clinical trial.

Study population is postmenopausal women with essential hypertension and osteopenia. The study will enroll 114 patients after screening (it is expected that 300 patients will need to be screened in order to reach this enrollment goal).

After the informed consent signing, the patient's participation in the study will include the period before the studied product administration, the treatment period and the final visit.

Patients will be randomized to one of two groups: moxonidine group or bisoprolol group.

According to the study protocol, patients randomization to the control and investigated groups will be carried out using a simple envelopes method and, therefore, it is assumed that the control and the investigated groups will be matched by the basic measured parameters; the number of subjects in the main and control groups is planned to be equal.

The study endpoints are measured prior to the studied product initiation (V1) and after completion of 48-week treatment with the investigated product (V4).

The period prior to the studied treatment initiation is designed to assess the patient meeting inclusion criteria and to carry out 7-10-day washout period in patients with previous antihypertensive therapy. The planned duration of the period before the treatment initiation does not exceed 14 days after the signing of the informed consent form by the patient.

Then, at the enrollment visit during the treatment period, the investigator will assess the patient meeting the inclusion criteria. If the inclusion criteria are met, the patient will be enrolled in the study. The baseline condition data will be obtained from the patient, and then the patient will be randomized to one of the two treatment groups (moxonidine or bisoprolol). The treatment period involves the enrollment visit (V1), and 3 more visits.

The final visit 4 is carried out at week 48 after the enrollment visit, the patient then completes the study.

The patients' treatment includes gradual titration of the studied products doses.

Group 1 will receive moxonidine with the dose titrated to a maximum, and then, if necessary, the patient will be shifted to the combination therapy (Step 2 – adding an ACE inhibitor)

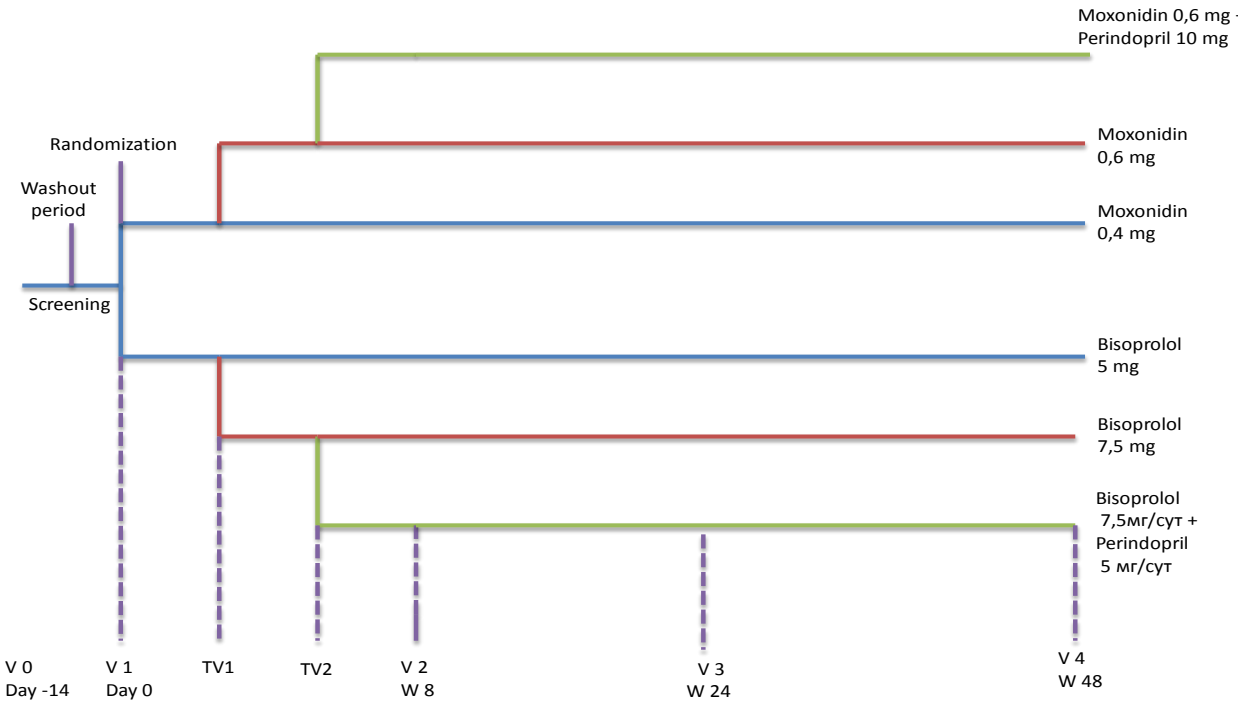
Group 2 will receive bisoprolol with the dose titrated to a maximum, and then, if necessary, the patient will be shifted to the combination therapy (Step 2 – adding an ACE inhibitor).

After randomization to moxonidine and bisoprolol groups (V1), patients start treatment with 0.4 mg moxonidine QD or 5 mg bisoprolol QD. If the target BP (<140/90 mmHg) is reached in 2 weeks, the patient continues taking the medication at the same dose. If the target BP is not reached in 2 weeks, the moxonidine dose is increased to 0.6 mg QD, the dose of bisoprolol is increased to 7.5 mg QD. If the target BP is not reached in 2 weeks of treatment with the increased doses, an ACE inhibitor (perindopril) at a dose of 10 mg/day is added at the 8th week of the study. In case of intolerance to perindopril, losartan at a dose of 50 mg/day will be administered.

During the study, the patient will have parameters of efficacy, tolerability and safety of the therapy with moxonidine or bisoprolol regularly assessed.

The study design is shown in Figure 1.

Figure 1. The overall study design



3.2 Patients randomization and identification

The study participants are randomized using a simple envelopes method. An independent person will generate a random table for 114 records in which 57 will be marked as "M" and 57 will be marked as "B". According this computer based randomization table cards with letter "B" or "M" will be sealed in 114 numbered envelopes. The randomization table will also be sealed in a separated envelope. The numbered envelopes will be sent to Principal Investigator. The envelope with randomization table will be stored in the Sponsor file.

Each patient is assigned with a special identification code that is only used in the program. The code is assigned to a patient after enrollment and includes the health care facility code and the patient number.

According to the protocol, decoding keys for the identification codes are not provided. Persons authorized by the Sponsor, health care or other regulatory authorities may inspect any program data available to the investigator.

3.3 Study duration

The total duration of the study is 48-50 weeks.

Patients' enrollment – 12 months. After screening period (1-14 days) and washout period (7-10 days), every patient will be treated for up to 48 weeks.

3.4 Schedule of the study procedures

Prior to the study enrollment, examination to assess conformity with the inclusion/exclusion criteria, to obtain baseline data and ensure washout period (if necessary) will be carried out for a patient. After enrollment and initiation of the investigated treatment, the study procedures will be conducted to assess product tolerability, safety, efficacy and patient compliance. All scheduled visits are mandatory. Washout period will be carried out only for patients with prior antihypertensive therapy. Each patient is to sign the informed consent prior to any study activities including screening / "examination to assess conformity with the in- and exclusion criteria.

Schedule of the study procedures is presented in Table 2.

	Visit 0 Screening	Visit 1	Visit 2	Visit 3	Visit 4
	Day-14…-1	Day 0	Week 8	Week 24	Week 48
Drug administration		+	+	+	+
Dose titration / treatment adjustment		+	+	+	
BP / HBR / Patients' diary analysis	+	+	+	+	+
ECG, K, Na	+			+	
Creatinine	+			+	
ALT/AST	+			+	
Parathyroid hormone	+				
X-ray densitometry, BMD	+				+
Total calcium, Phosphorus	+			+	+
PWV		+			+
IMT + evaluation of subclinical atherosclerosis		+			+
Telomerase activity		+			+
Osteocalcin		+		+	+
Collagen type 1 C-telopeptide		+		+	+
Osteoprotegerin, RANKL		+			+
Safety Information	+	+	+	+	+

3.5 Number of patients:

114 patients will be enrolled to the study to ensure the final sample size. The patients will be randomized to one of two treatment groups (moxonidine group or bisoprolol group) using simple

randomization envelopes. It is anticipated that a screening of 300 subjects will be needed in order to enroll the minimum of 100 patients to the study.

According to the study protocol, patients randomization to the control and investigated groups will be carried out randomly and, therefore, it is assumed that the control and the investigated groups will be matched by the basic measured parameters; the number of subjects in the main and control groups is planned to be equal.

The study endpoints are measured prior to the studied product initiation (V1) and after completion of 48-week treatment with the investigated product (V4).

3.6 Study procedures

3.6.1 Screening and washout periods (V0)

Any patient screening procedures are conducted only after the informed consent to participate in the study is signed. After the informed consent is signed, the patient is assigned with a screening number and **the following procedures** are performed.

The investigator collects patient demographic data (gender, age), significant life history, detailed medical history (duration of hypertension, current antihypertensive drugs and duration of their use), and assesses hypertension severity and grade according to the ESH/ESC recommendations that are listed in Appendix 1. The investigator asks questions about the patient's history of cardiovascular disorders and other significant comorbidities and their treatment.

The researcher gathers information about medications that patient’s used during 30 days prior to the screening, asks about intolerance to antihypertensive drugs, especially I1-imidazoline receptors, beta-blockers and ACE inhibitors.

After the conversation with the patient, the investigator conducts a physical examination of organs and organ systems that must include measurement of heart rate, systolic and diastolic blood pressure according to ESH/ESC recommendations that are listed in Appendix 1 [17]. BP is first measured on the right and left arms. Thereafter, during the remaining study period, blood pressure should be measured at the arm with the highest blood pressure on screening. Resting heart rate (bpm) is measured by the standard method used in the physician routine practice. It is recommended to count heart rate for 60 seconds in a sitting position after 5 minutes of rest three times with 2-3 minutes interval between the measurements.

Blood pressure and heart rate are measured in a sitting position after 5 minutes of rest. **Three** measurements are carried out, the average value of the measurements is recorded.

The patient will have the resting standard 12-lead ECG registered. The investigator will record all clinically significant ECG abnormalities.

If the data obtained meet the screening criteria, biochemical (potassium, sodium, creatinine, total calcium, inorganic phosphorus, ALT, AST) and hormone (PTH) fasting blood tests will be conducted for the patient.

Results of the tests (CBC, BMP, pregnancy test) should be obtained prior to the washout period initiation and patient enrollment to verify compliance with screening criteria.

Dual energy X-ray absorptiometry to determine BMD and detect osteopenia will be performed.

After screening investigation results are obtained, if the patient meets screening criteria, the investigator:

- Schedules visit V1 for primary patients and patients who were only administered with fast acting antihypertensives to relieve a hypertension episode;
- Starts washout period for patients taking antihypertensive drugs at the time of screening visit, before proceeding to visit V1.

During the washout period, the investigator will ask the patient to refrain from taking her prior antihypertensives and other antihypertensives. The investigator may prescribe the patient with short acting antihypertensives to relieve a hypertension episode (at the investigator discretion: nifedipine, captopril or other acting products for urgent blood pressure lowering).

Also, a modified lifestyle will be advised, e.g., dieting (according to ESH/ESC recommendations that are listed in Appendix 3), cessation of smoking, physical exercises.

For washout period conditions and requirements please refer to "Treatment of patients".

If the patient does not meet the screening criteria, she should not proceed with the following visits and her data and reason for withdrawal from the study are recorded in the screened patients accountability form.

3.6.2 Enrollment visit (V1)

Enrollment visit is conducted no later than 14 days after signing the informed consent form by the patient.

The investigator documents all significant changes in the history of hypertension and concomitant treatment (including fast acting antihypertensives to relieve a hypertension episode that may be administered during the washout period); the investigator identifies and documents adverse events associated with the protocol procedures, if any, starting from the date of the informed consent signing.

The investigator conducts a physical examination of the patient by organs and organ systems that must include measurement of heart rate, systolic and diastolic blood pressure according to ESH/ESC recommendations that are listed in Appendix 1 [17]. Blood pressure and heart rate are measured in a sitting position after 5 minutes of rest on the arm with the highest BP during screening. Three measurements are done; the average value of the measurements is documented. The investigator assesses hypertension severity and grade according to the ESH/ESC recommendations that are listed in Appendix 2.

Applanation tonometry method is used to measure changes in patient's PWV; duplex ultrasonography of extracranial brachiocephalic arteries is employed to evaluate IMT and subclinical atherosclerosis.

Blood is sampled to investigate bone metabolism: osteocalcin, Ctx, OPG, RANKL.

Blood is sampled to determine telomerase activity.

The investigator may enroll the patient in the study and start the investigated treatment only if the patient meets all the screening criteria to start the treatment.

The investigator randomizes patients to one of two treatment groups by means of the simple envelopes method.

Treatment regimens

- **Group 1** patients receive moxonidine with dose titration up to the maximum, then a patient may be switched to the combination therapy, if necessary (step 2 - adding an ACE inhibitor).
- **Group 2** patients receive bisoprolol with dose titration up to the maximum, then a patient may be switched to the combination therapy, if necessary (step 2 - adding an ACE inhibitor).

The investigator will provide a Group 1 patient with moxonidine 0.4 mg in the amount required for 56 days of treatment plus 7 extra days and additionally moxonidine 0.2 mg in an amount required for 42 days of treatment if the dose is titrated up to 0.6 mg/day.

The patient will take the first moxonidine tablet immediately during the visit after all the visit procedures are completed. The patient will be instructed to take 1 tablet of moxonidine 0.4 mg in the morning, daily. The next visit will be scheduled in week 8 after the enrollment visit (in 56 days ± 5 days after the enrollment visit).

The patient will be asked to bring all the blisters of investigated product (empty, started and not started blisters) to every visit after the study initiation.

The investigator will give the patient blood pressure self-monitoring diary which is to be used by the patient to daily document her BP values and to bring it to every subsequent visit.

3.6.3 Telephone visits (TV1 and TV2)

Telephone visits are conducted at week 2 and week 4 after the enrollment visit. The investigator will document the disease history since the last visit, including all adverse events and changes in concomitant treatment.

On the 2nd week telephone visit **(TV1),** the investigator evaluates efficacy, safety and tolerability of the investigated treatment. Patients will continue to take moxonidine 0.4 mg/bisoprolol 5 mg until visit V2. If BP control is insufficient, the investigator may increase moxonidine and bisoprolol doses to 0.6 mg and 7.5 mg QD, respectively.

On the 4th week telephone visit **(TV2),** the investigator evaluates efficacy, safety and tolerability of the investigated treatment. Patients will continue to take moxonidine 0.6 mg/bisoprolol 5 mg until visit V2. If BP control is insufficient with moxonidine 0.6 mg/bisoprolol 7.5 mg QD, the investigator adds perindopril 10 mg QD.

3.6.4 Visit 2 (V2)

Visit 2 is conducted at week 8 after the enrollment visit. The investigator will document the disease history since the last visit, including all adverse events, changes in concomitant treatment, and changes in concomitant medications doses, if any.

The investigator will analyze the effectiveness of the therapy according to the patient's BP self-monitoring diary data.

The investigator measures blood pressure and heart rate in a sitting position after 5 minutes of rest. **Two** measurements are done; the average value of the measurements is documented. BP is measured on the same arm during the entire study.

The investigator analyzes the patient's compliance based on the number of returned tablets.

The investigator evaluates response to the treatment (target BP reaching), documents it in source documents and decides on further treatment of the patient. If target BP has not been reached, the patient's investigated product dose is titrated according to the study design. If the target BP has been reached, the patient continues with the current treatment until the next visit.

The investigator will invite the patient to the next visit (visit V3) scheduled for week 24 after the enrollment visit (168 days ± 5 days after the enrollment visit); the patient will be asked to return the investigated medication blisters (empty, started and not started blisters). The patient will be instructed to start taking the provided product the next day morning, 1 tablet per day. The patient will be instructed to report any adverse events (if applicable) to the investigator.

3.6.5 Visit 3 (V3)

The investigator will document the disease history since the last visit, including all adverse events, changes in concomitant treatment, changes in concomitant medications doses, if any.

The investigator will analyze the effectiveness of the therapy according to the patient's BP self-monitoring diary data.

The investigator measures BP and HR according to the ESH/ESC recommendations that are listed in Appendix 1. Blood pressure and heart rate are measured in a sitting position after 5 minutes of rest. **Two** measurements are done, the average value of the measurements is documented. BP is measured on the same arm during the entire study.

Fasting blood sampling will be carried out for the following tests: BMP (potassium, sodium, creatinine, total calcium, inorganic phosphorus, ALT, AST), hormonal test (PTH) and bone metabolism tests, including osteocalcin, Ctx, OPG, RANKL.

The investigator evaluates response to the treatment (target BP reaching), documents it in source documents and decides on further treatment of the patient. If target BP has not been reached, the patient's investigated product dose is titrated according to the study design. If the target BP has been reached, the patient continues with the current treatment until the next visit.

The investigator analyzes the patient's compliance based on the number of returned tablets. The investigator will provide the patient with the investigated medications and invite the patient to the next visit (visit V4) scheduled for week 48 after the enrollment visit (336 days ± 5 days after the enrollment visit); the patient will be asked to return the investigated medication blisters (empty, started and not started blisters). The patient will be instructed to start taking the provided product the next day morning, 1 tablet per day. The patient will be instructed to report any adverse events (if applicable) to the investigator.

3.6.6 Final visit (V4)

The investigator will document the disease history since the last visit, including all adverse events, changes in concomitant treatment, changes in concomitant medications doses, if any.

The investigator will analyze the effectiveness of the therapy according to the patient's BP self-monitoring diary data.

The investigator measures BP and HR according to the ESH/ESC recommendations that are listed in Appendix 1. Blood pressure and heart rate are measured in a sitting position after 5 minutes of rest. Two measurements are done; the average value of the measurements is documented. BP is measured on the same arm during the entire study. Full physical examination is not required.

Patient's biochemical blood analysis (total calcium, inorganic phosphorus) is performed. Blood is sampled to investigate bone metabolism: osteocalcin, Ctx, OPG, RANKL.

Blood is sampled to determine telomerase activity.

Dual energy X-ray absorptiometry to determine BMD and detect osteopenia is performed.

Applanation tonometry method is used to measure changes in patient's PWV; duplex ultrasonography of extracranial brachiocephalic arteries is employed to evaluate IMT and subclinical atherosclerosis.

The investigator evaluates the response to the treatment (target BP reaching) and documents it in the source documents, as well as estimates patient compliance based on amount of the returned investigated product.

After successful completion of visit V4 procedures, the patient completes her participation in the study. The investigated product is discontinued; further treatment is carried out according to the attending physician advice.

3.7 Description of individual procedures

Laboratory testing

The investigator must warn a patient to come to the scheduled study visits after fasting to have her blood sampled for laboratory testing.

Table 2. Method and frequency of laboratory testing

Test	Parameters	Laboratory	Method	Frequency
Blood biochemistry	Creatinine* Potassium Sodium ALT AST Total calcium Inorganic phosphorus	Site	Adopted at the hospital center	2x: visits V0 and V3
Blood biochemistry	Total calcium Inorganic phosphorus	Site	Adopted at the hospital center	3x: visits V0, and V3, V4
Hormonal blood test	Parathyroid hormone	Site	Adopted at the hospital center	1x: visit V1
Bone metabolism	Osteocalcin Ctx	Site	Adopted at the hospital center	3x: visits V1, V3, V4
	OPG RANKL	Site	Adopted at the hospital center	2x: visits V1, V4

*Creatinine clearance (CC) is calculated by **Cockcroft-Gault** equation on visits V0 and V3:

CrCl = (140 - age) x IBW / (Scr x 0,792) (x 0.85 for females)

If creatinine was measured in mg/dl, to convert the value to mkmol/L it should be multiplied by 88.4.

3.8 Study products

Investigated products, moxonidine and bisoprolol, will be provided by the Sponsor, packaged and labeled in accordance with local regulatory requirements.

3.8.1 Investigated product:

Name: I1-imidazoline receptor agonist, INN: moxonidine

Manufactured by Rottendorf Pharma GmbH, Germany, packaged and released by Abbott Healthcare SAS, France

Pharmaceutical form: 0.4 mg and 0.2 mg coated tablets manufactured by Rottendorf Pharma GmbH, Germany, packaged and released by Abbott Healthcare SAS, France.

One tablet contains 0.40 mg moxonidine as an active substance and the following excipients: lactose monohydrate - 95.60 mg; povidone K25 - 0.70 mg; crospovidone – 3.00 mg; magnesium stearate - 0.30 mg; hypromellose 6mPas - 1.300 mg; ethyl cellulose aqueous Disp.30% - 4.000 mg (solids 1.200 mg) ; macrogol 6000 - 0.250 mg; talc - 0.875 mg; red ferric oxide (E172) - 0.125 mg; titanium dioxide (E171) - 1.250 mg. There are 14 tablets in the blister; the carton contains 1, 2 or 7 blisters.

One tablet contains 0.20 mg moxonidine as an active substance and the following excipients: lactose monohydrate - 95.80 mg; povidone K25 - 0.70 mg; crospovidone – 3.00 mg; magnesium stearate - 0.30 mg; hypromellose 6mPas - 1.300 mg; ethyl cellulose aqueous Disp.30%- 4.000 mg (solids 1.200 mg); macrogol 6000 - 0.250 mg; talc - 0.9975 mg; red ferric oxide (E172) - 0.0025 mg; titanium dioxide (E171) - 1.250 mg. There are 14 tablets in the blister; the carton contains 1, 2 or 7 blisters.

Posology and method of administration: Moxonidine is taken orally, once-twice a day, regardless of meals. Maximum daily dose of moxonidine is 0.6 mg.

Duration of treatment: Moxonidine 0.4 mg QD is prescribed to postmenopausal patients with hypertension and osteopenia. Subsequently, in patients with no response, the daily dose is titrated up to 0.6 mg; then perindopril 10 mg may be added to the regimen at week 8, if necessary. Patients should take the medication until study week 48 (V4).

3.8.2 Comparative product

Name: Cardioselective $beta_1$ blocker. INN: Bisoprolol.

Produced by Merck KGaA, Germany

Pharmaceutical form: film-coated tablets.

One tablet contains bisoprolol hemifumarate and bisoprolol fumarate (2: 1) as active substances 5 mg, and the following excipients: calcium hydrogen phosphate anhydrous - 132 mg; corn starch fine powder - 14.5 mg; colloidal anhydrous silica - 1.5 mg; MCC - 10 mg; crospovidone - 5.5 mg; magnesium stearate - 0.97 mg, film coating: hypromellose 2910/15 - 2.2 mg; macrogol 400 - 0.53 mg; dimethicone 100 - 0.11 mg; iron oxide yellow dye (E172) - 0.02 mg; titanium dioxide (E171) - 0.97 mg.

Posology and method of administration: Bisoprolol is taken orally, once a day, regardless of meals.

Duration of treatment: Bisoprolol 5 mg is prescribed to postmenopausal patients with hypertension and osteopenia. Subsequently, in patients with no response, the daily dose is titrated up to 7.5 mg every 2 weeks; then perindopril 10 mg may be added to the regimen at week 8, if necessary. Patients should take the medication until study week 48 (V4).

3.8.3 Additional medications

3.8.3.1 Name: angiotensin converting enzyme inhibitor. INN: perindopril

Produced by Les Laboratoires Servier Industrie

Pharmaceutical form: film-coated tablets.

One tablet contains perindopril arginine 10 mg as an active substance. Other ingredients: lactose monohydrate, magnesium stearate, maltodextrin, hydrophobic colloidal silica, sodium starch glycolate (type A), glycerol, hypromellose, macrogol 6000, titanium dioxide (E171), copper chlorophyllin (E141 II).

Posology and method of administration: once a day, orally, before a meal, preferably in the morning.

Duration of treatment: perindopril 10 mg is prescribed to postmenopausal patients with hypertension and osteopenia who have not reached target BP (<140/90 Hgmm) by V2 (week 8). Patients should take the medication until study week 48 (V4).

3.8.4 Name: angiotensin II receptor blocker. INN: Losartan

Produced by Berlin-Chemie, Germany.

Pharmaceutical form: coated tablets.

Each tablet contains 50 mg of losartan.

Posology and method of administration: Bisoprolol is taken orally, once a day, regardless of meals. The product is prescribed to postmenopausal patients with hypertension and osteopenia non-responsive to moxonidine or bisoprolol monotherapy for 4 weeks and intolerant to perindopril. Patients should take the medication until study week 48 (V4).

3.8.5. Name: calcium and vitamin D. INN: Calcium carbonate + cholecalciferol

Produced by Nycomed Pharma, Norway.

Pharmaceutical form: chewable tablets.

Each tablet contains the following active ingredients calcium carbonate 1250 mg (equivalent to 500 mg of elemental calcium), cholecalciferol (vitamin D_3) 5 mcg (200 IU) (as cholecalciferol concentrate - 2 mg), *excipients:* sorbitol - 390 mg; isomalt - 62 mg; povidone - 36.4 mg; magnesium stearate - 6 mg; aspartame - 1 mg; orange oil - 0.97 mg; mono- and diacylglycerols - 0.0008 mg.

Posology and method of administration: the product is taken orally during meals, it should be chewed or dissolve in the mouth.

3.9 Product packaging and storage

3.9.1 Packaging.

Moxonidine is packaged in original factory blisters; every blister contains 14 tablets.

Bisoprolol is packaged in original factory blisters; every blister contains 10 tablets either every blister contains 50 tablets.

At every visit (V1, V2, V3), the investigator will provide a patient with the product blisters for subsequent treatment period till next visit.

Storage conditions. Moxonidine and bisoprolol do not require any special storage conditions.

3.9.2 Products counting procedures

The investigator analyzes the patient's compliance based on the number of returned tablets at visits 2, 3 and 4.

3.10 Study endpoints

Primary endpoint:

- Changes in mean values of the bone resorption marker (collagen type 1 C-telopeptide) at the end of the study (V4) from the baseline (V1) in comparison between the groups.

Secondary Endpoints:

- To assess mean values of osteocalcin at visit 4 versus baseline level (visit 1) and to compare the values between the groups
- To assess mean values of the receptor activator of nuclear factor kappa-B ligand (RANKL) at visit 4 versus baseline level (visit 1) and to compare the values between the groups
- To assess mean values of BMD at visit 4 versus baseline level (visit 1) using control dual-energy X-ray absorptiometry and to compare the results between the groups
- To assess mean telomerase activity at visit 4 versus baseline level (visit 1) and to compare the values between the groups
- To assess mean pulse wave velocity (PWV) at visit 4 versus baseline level (visit 1) and to compare the values between the groups
- To assess mean intima-media thickness (IMT) at visit 4 versus baseline level (visit 1) and to compare the values between the groups
- To estimate the proportion (%) of patients who achieved target blood pressure <140/90 mmHg at the visit 2 (Week 8), 3 (Week 24) and 4(Week 48) and according to the patient's diary.

4 PATIENT SCREENING AND EXCLUSION

4.1 Patient Population

Postmenopausal women with essential hypertension and osteopenia treated with moxonidine.

4.2 Inclusion criteria

A patient should meet all of the following inclusion criteria:

1. Females aged 45 years and older
2. Postmenopausal (absence of menstrual periods for a minimum of 12 months) at the moment of Informed Consent sign.
3. Arterial hypertension grade I / II per ESH/ESC 2013 guidelines (diastolic pressure ≥ 90 and <110 mm Hg, systolic pressure ≥140 and <180 mm Hg).
4. Not achieving BP targets <140/90 mmHg either during antihypertensive therapy or naive.
5. Absence of moxonidine or bisoprolol treatment at least 6 months before the study
6. Osteopenia of lumbar spine and/or proximal part of the femur (osteoporosis T-score from -1 to -2.5 standard deviations [SD]) by X-Ray densitometry.
7. .Signed informed consent form to participate in the program.

4.3 Exclusion criteria

A patient must not meet any of the following exclusion criteria:

1. Hypersensitivity to moxonidine, bisoprolol or any other ingredient of the respective formulations
2. Any Contraindications for moxonidine, bisoprolol
3. Osteoporosis (T-score below - 2.5 SD).
4. Primary or secondary hyperparathyroidism.
5. Paget's disease of bones.
6. History of low traumatic bone fractures.
7. Malabsorption syndrome.
8. History of gastro-intestinal surgery.
9. Severe disturbance of peripheral circulation.
10. Raynaud's disease.
11. Symptomatic (secondary) hypertension (caused by any primary internal diseases)

12. Morbid obesity (BMI over 40 kg/m2).
13. Symptoms of estrogen deficiency such as hot flushes, nights sweat, vaginal dryness
14. Administration of any hormone-replacement therapy (HRT) or intake of isoflavones
15. Secondary hypogonadism.
16. SistBP ≥180 mm Hg and/or DiastBP ≥110 mm Hg.
17. Clinical presentations of cardiovascular disease: coronary heart disease (CHD), history of stroke, transient ischemic attack (TIA), Charcot's syndrome.
18. Severe heart failure.
19. Hemodynamically significant congenital heart disease.
20. Heart rhythm disorders which require permanent use of any antiarrhythmic medications (including β-adrenoblockers and calcium antagonists).
21. Diabetes mellitus of any genesis.
22. Severe liver failure.
23. Severe kidney failure including patients on dialysis
24. Thyroid diseases accompanied by functional disorders (thyrotoxicosis or uncompensated hypothyroidism).
25. Alcohol and drug abuse.
26. Patients with oncological diseases diagnosed within 5 years before IC execution.
27. Inability of the patient to comprehend the essence of the program and to provide his/her consent for participation in the program.
28. Patients with any condition, which in the opinion of the Investigator makes the patient unsuitable for inclusion based on clinical judgment.
29. Corticosteroid therapy
30. Participation in any other clinical study during the whole course of this investigation including participation in a study within 30 days prior to providing the informed consent for this trial

4.4 Start of treatment criteria

Start of investigated treatment (i.e., patient enrollment to the study) is possible when all of the following conditions are met during the enrollment visit:

1. Patient is to meet all the inclusion criteria and should lack any of the exclusion criteria.

2. Patients previously treated with antihypertensive agents have undergone 7-10-day washout period according to the protocol (all antihypertensive drugs are discontinued, except fast-acting agents to relieve hypertensive episodes).

4.5 Study withdrawal criteria

A patient may be withdrawn from the study before the treatment is started, if the investigator discovers deviations from any inclusion criteria, exclusion criteria, or criteria for the treatment initiation. Patients who withdrew before the treatment start (i.e., during screening or washout period), will be substituted with new patients.

In the present study, withdrawal from the study will also mean discontinuation of the investigated treatment.

The patient may be withdrawn from the study due to the following reasons:

1. Withdrawal of the informed consent to participate in the study.
2. Low treatment compliance (<80%).
3. Adverse events that in the investigator's opinion make the treatment continuation impossible, dangerous, or inconsistent with best patient interest and safety. A SAE is not necessarily the cause of early patient withdrawal from the study.
4. According to the investigator, continued participation of the patient in the study threatens the patient's safety.
5. It is necessary to administer treatment prohibited by the study protocol.
6. Failure of the investigated treatment (i.e., recurrent rise of blood pressure ≥180/120 mmHg after previously achieved target BP level).
7. Death of the patient.
8. Sponsor decision.

4.6 Early withdrawal procedures

All patients who were withdrawn from the study early are asked to complete the final visit procedures, if possible. If the decision to terminate the patient participation was made between two scheduled visits, the patient is asked to come for the upcoming scheduled visit, as usual, or make an unscheduled visit.

The reason for the early withdrawal should be indicated in the source documents. If the patient is lost to follow-up, the investigator should make all reasonable efforts to contact the

patient to obtain information on date of withdrawal and reason for the investigated product discontinuation. If the patient cannot be reached, she will be considered as lost to follow-up.

In the case of early investigated product discontinuation due to an adverse event (regardless of whether the event should be immediately reported), the researcher must make every effort to collect information regarding the AE outcome. This information is added to the source documents and CRF, under adverse events section.

5 Treatment of patients

5.1 Prescribed treatment

Treatment assignment at the study visits

Washout period is designed for patients who have already been taking antihypertensive medications. All antihypertensive medications are discontinued 7-10 days prior to the enrollment visit. The patient is asked to refrain from taking these and any other antihypertensive medications during the washout period. The average duration of the washout period is 7 days. The investigator may shorten the duration of the washout period, but it should not be shorter than 6 half-life periods ($T_{1/2}$) of the antihypertensive medications patient was taking.

During the washout period, the patient may be administered with fast-acting agents to relieve hypertensive episodes (at the investigator's discretion – nifedipine, captopril). The period from the last dose of these antihypertensives to the enrollment visit must be at least 6 $T_{1/2}$ of these agents (e.g., 18 hours for nifedipine).

If the above conditions are not met, the patient is withdrawn from the washout period and will not participate in the study. The researcher may at any time terminate the washout period, if the patient does not tolerate it well.

The washout period is not required for patients who were not previously treated with antihypertensives, and patients who were not receiving antihypertensives at the time of the screening. If the patient was treated with any antihypertensives earlier and discontinued the medications **before** the screening, the washout period is not necessary for her, if the period between the last dose of the antihypertensives and the enrollment visit is not shorter than 6 $T_{1/2}$ of these drugs.

All enrolled patients are randomized in the two study groups (moxonidine group or bisoprolol group).

All group 1 patients are prescribed with moxonidine 0.4 mg monotherapy. At the **V1 enrollment visit**, the patient will be given the medication and will take first dose of moxonidine in the presence of the investigator. Thereafter, patients will take the medication every morning, during the entire study. The medication will be dispensed to a patient at visits V1, V2, V3, and the patient will start taking the drug on her own on the day following the visit. One tablet of the investigated product should be taken daily, in the morning, regardless of meals.

On 2nd week telephone visit, the investigator evaluates efficacy, safety and tolerability of the investigated treatment. Patients will continue taking moxonidine 0.4 mg QD until next visit V2. If BP control is insufficient, the investigator may increase moxonidine dose to 0.6 mg QD.

On 4th week telephone visit, the investigator evaluates efficacy, safety and tolerability of the investigated treatment. Patients will continue taking moxonidine 0.4 mg (0.6 mg) QD until next visit V2. If BP control is insufficient with moxonidine 0.6 mg QD, the investigator adds perindopril 10 mg QD.

All group 2 patients are prescribed with bisoprolol 5 mg monotherapy. At the **V1 enrollment visit**, the patient will be given the medication and will take first dose of bisoprolol in the presence of the investigator. Thereafter, patients will take the medication every morning, during the entire study. The medication will be dispensed to a patient at visits V1, V2, V3, and the patient will start taking the drug on her own on the day following the visit. One tablet of the investigated product should be taken daily, in the morning, regardless of meals.

On 2nd week telephone visit, the investigator evaluates efficacy, safety and tolerability of the investigated treatment. Patients will continue to take bisoprolol 5 mg until visit V2. If BP control is insufficient, the investigator will increase bisoprolol dose to 7.5 mg QD.

On 4th week telephone visit, the investigator evaluates efficacy, safety and tolerability of the investigated treatment. Patients will continue to take bisoprolol 5 mg (7.5 mg) until next visit V2. If BP control is insufficient with bisoprolol 7.5 mg QD, the investigator adds perindopril 10 mg QD.

At visit V2:

- If a patient responds to the selected treatment regimen (BP <180/120 mmHg), the investigator will continue this regimen until the next visit.
- If a patient does not respond to the selected treatment regimen (BP ≥180 /120 mmHg), the patient is withdrawn from the study.

At visit V3:

- If a patient responds to the selected treatment regimen (BP <180/120 mmHg), the investigator will continue this regimen until the next visit.
- If a patient does not respond to the selected treatment regimen (BP ≥180/120 mmHg), the patient is withdrawn from the study.

At final visit V4, the investigator will evaluate the patient response to the treatment and will discontinue all investigated medications. Further treatment is carried out according to the attending physician advice.

5.2 Fast-acting agents to relieve hypertensive episodes

During the washout period and the rest of the study, use of short-acting agents to relieve hypertensive episodes, such as captopril and nifedipine, is allowed. However, patients must be instructed to refrain from these medications for 24 hours prior to the study visit in order to obtain accurate blood pressure data. At the visits, the investigator will ask if a patient took any short-acting drugs to relief hypertensive episodes; data and time of the last dose will be documented in the CRF.

5.3 Investigated treatment withdrawal

If the investigated treatment should be withdrawn for any reason before the end of the study, gradual investigated products doses reduction is not required. The early treatment withdrawal means the patient is withdrawn from the study.

5.4 Permitted and prohibited treatment

5.4.1 Permitted treatment

Patients with comorbidities may continue taking previously prescribed medications. Patients will be asked to report any medications and dietary supplements they were taking within a month prior to the screening or have taken during the study. The investigator will document any medication the patient is taking in the source documents and CRF.

Additionally, it is recommended to avoid nonsteroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, and ascorbic acid at a dose >3 g/day due to the increased risk renal function impairment.

5.4.2 Prohibited treatment

During the treatment with the investigated product, patients **should not take**:

- Other antihypertensive drugs, except for the investigated products. The only exception is short-acting antihypertensives prescribed by the investigator to relieve hypertensive episodes PRN. These medications should be withheld the day prior to the visit to avoid effects on blood pressure measurement during the visit and evaluation of the investigated treatment efficacy.
- Thiazide diuretics, corticosteroids, bisphosphonates or levothyroxine since these agents are known to affect bone metabolism and BMD.
- Antacids, if the interval between an antacid and the investigated product administration is less than 2 hours.

If there is a need to prescribe the prohibited treatment to a patient or it became known that a patient is receiving the prohibited treatment, the patient is withdrawn from the study.

5.5 Analysis of compliance

At every visit, starting with visit V2, the dispensed and returned investigated product is counted, and the patient compliance is assessed. The investigator or his/her authorized representative will count the number of dispensed and returned tablets and document it in the accountability form and CRF. Additionally, date of the first and last product administration, and deviations in the product dosing regimen within the last intervisit interval (if any) will be documented in CRF.

In case of low patient compliance with the investigated treatment (the patient took <80 tablets within the intervisit interval), the patient will be withdrawn from the study.

5.6 Patient supply and return of the product

The investigated products moxonidine and bisoprolol are intended only for patients participating in the study and should be used according to the protocol.

The patient will be provided with the required amount of the product at the enrollment visit (V1), visit V2, and visit V3 for subsequent treatment period till next visit.

The product will be provided to the patient in the course of the study only. The treatment will be discontinued at final visit V4.

The patients will be asked to bring all used and unused investigated products blisters to the study site at visits V2, V3, V4.

All defects and damages of the investigated product or its packaging must be reported to the study CRA. Additionally, the investigator must report any patient complaints to the study CRA (change in the product taste, appearance, etc.).

5.7 Product accountability

The investigator and/or pharmacist and/or authorized site staff is responsible for the product accountability. The product accountability will be monitored by the CRA on a regular basis.

Sponsor will provide the investigated product accountability forms to document all the product shipments, distribution and return. The investigator and/or pharmacist and/or authorized site staff should fill out these forms in a timely manner. CRA must fill out the product return and disposal form after the end of the study.

6 EFFICACY EVALUATION

Efficiency analysis will be carried out in the population of patients who completed the study according to the protocol.

6.1 Primary endpoint efficacy criteria:

Changes in mean values of the bone resorption marker (collagen type 1 C-telopeptide) at the end of the study (V4) from the baseline (V1) in comparison between the groups.

6.2 Secondary endpoints efficacy criteria:

1. Changes in mean values of the bone synthesis marker (osteocalcin) at the end of the study (V4) from the baseline (V1) and to compare the values between the groups.

2. Changes in mean values of the receptor activator of nuclear factor kappa-B ligand (RANKL) at visit 4 versus baseline level (visit 1) and to compare the values between the groups

3. Changes in mean values of BMD at visit 4 versus baseline level (visit 1) using control dual-energy X-ray absorptiometry and to compare the results between the groups

4. Changes in mean values of telomerase activity at visit 4 versus baseline level (visit 1) and to compare the values between the groups

5. Changes in mean values of pulse wave velocity (PWV) at visit 4 versus baseline level (visit 1) and to compare the values between the groups

6. Changes in mean values of intima-media thickness (IMT) at visit 4 versus baseline level (visit 1) and to compare the values between the groups

7. Proportion of the treatment responders (defined as the proportion (%) of patients who achieved target blood pressure <140/90 mmHg) after 8 and 48 weeks of the investigated treatment (V2, V3 and V4) and to compare the values between the groups.

7 SAFETY EVALUATION

7.1 Safety parameters

The safety parameters that are measured at every study visit are shown in Table 2. The investigator will collect required data including:

1) documentation of significant medical history at the screening visit the following visits,

2) identification and documentation of adverse events, including abnormalities identified with:

a) physical examination,

b) laboratory tests.

The investigator will collect and interpret all relevant information and make a decision on whether to report any deviation from the norm, as an adverse event.

7.2 Methods and timing

Methods and timing of the parameters identification are as follows:

Physical examination. During the patient screening and enrollment and at the final visit, the investigator will document the patient's complaints and abnormalities, detected on

physical examination. All clinically significant abnormalities should be reported as adverse events.

Blood pressure and heart rate. All patients will have their blood pressure and heart rate measured at every visit. If blood pressure and heart rate are abnormal, the investigator will evaluate the clinical significance of the abnormality and decide on whether to document it as an adverse event.

Laboratory tests parameters: creatinine (including creatinine clearance calculation according to Cockcroft-Gault equation), potassium, sodium, ALT, AST. Fasting blood samples will be obtained at screening and at the final visit. Results of the tests will be entered into the CRF. If the sample is lost, the investigator may order resampling if medically indicated (e.g., if invalid test results are suspected).

All clinically significant adverse deviations from the baseline (screening) will be reported as adverse events.

8 ADVERSE EVENTS

Definitions

8.1 Adverse event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, including laboratory parameters deviations. AE does not necessarily have a causal relationship with the treatment.

Causal relationship with investigated treatment

The AE(s) relationship with investigated product(s) will be assessed according to the following categories:

1. The relationship is considered **certain** if an AE developed during the treatment with the product and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. The relationship is considered **probable** if an AE occurred in a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other

drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

3. The relationship is considered **possible**, if an AE occurred in a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

4. The relationship is considered **unlikely**, if a causal relationship of an AE with the drug cannot be ruled out, but:

- other drugs, chemicals or underlying disease provide plausible explanations,

- temporal relationship of the AE to the drug administration is improbable.

5. AE is considered **unrelated** to the drug administration, if:

- there is a clear alternative explanation of the AE, and/or

- temporal relationship of the drug and the AE is groundless, and/or

- relationship of the drug with the AE is not plausible.

6. The relationship is considered **unassessable**, if the data is insufficient or contradictory and cannot be supplemented or verified.

8.2 Adverse reaction (AR)

Adverse reaction (AR) means a noxious and unintended response to an investigated medical product, **associated** with any dose of the product.

According to the “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" (April 2006), all adverse events, regarded by an investigator or Sponsor as **having reasonable causal relationship with the medicinal product** are considered AR, that is related to the investigated product.

Based on the above definitions, ARs are all AEs with the following relationship with the investigated product:

1 - Certain

2 - Probable

3 - Possible

4 - Unassessable

AE is not considered AR if relationship with the drug is estimated as:

5 - Unknown

6 - Unrelated

Seriousness criteria

AE/AR is considered serious if it:

- Results in death,
- Is a life-threatening event;

Note: AE is not considered to be life-threatening if the subject's life was in danger during the AE; this does not apply to events that hypothetically could have led to death if they progressed.

- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Leads to persistent and significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important from a medical point of view event that may pose a risk to the patient or may require intervention to prevent one of the outcomes described above. All suspected cases of infectious agents transmission via medicinal product are considered serious and should be evaluated in the category of "medically significant events" if there are no other seriousness criteria.

AE/AR is **not** considered serious if:

- The event does not meet conditions described in the definition of serious AE/AR.

Adverse event (AE) / adverse reaction (AR) severity

The severity of serious and non-serious AE or AR should be evaluated according to the following criteria.

- Mild: no intervention or routine actions are required; for laboratory parameters, abnormality is considered mild.
- Moderate: no intervention or routine actions are required; for laboratory parameters, abnormality is considered moderate.

- Severe: intervention or routine actions are required; for laboratory parameters, abnormality is considered severe.

Adverse event (AE) / adverse reaction (AR) expectedness criteria

AE/AR is considered unexpected, if its nature, seriousness or outcome does not correspond with the Reference safety document (there must be ONLY ONE Reference safety document defined by the Protocol, and Clinical trial appendices; it should be referred to in the protocol and appendix cover letters).

If the product has already been issued a registration certificate (RC), the Reference safety document is the Summary of product characteristics (SPC). If there are multiple versions of the SPC (e.g., if there are national product RCs), the most appropriate version of the SPC should be provided.

If the product has never been issued with a registration certificate, the Reference safety document is the Investigator's Brochure (IB).

8.3 Suspected unexpected serious adverse reaction (SUSAR)

Any serious unexpected adverse events, considered by an Investigator or Sponsor as associated with the product are qualified as unexpected AR (SUSAR). SUSARs should be reported according to the instructions in Section 8.4.

8.4 Adverse events monitoring and reporting

At each study visit, the investigator will assess any subjective or objective AEs. AEs identified based on complaints of a patient, patient's relatives/legal representatives, over phone, in writing or by e-mail will also be documented. In such cases, the investigator should try to assess the AE and obtain medical conformation.

In case of AE, the investigator must document the AE in the special CRF section "Adverse event form"; a new page should be used for every AE, the investigator should assess causal relationship of the AE and the product regardless of whether the AE is serious or not, whether it is associated with the drug, discovered by the investigator or patient.

All available information and results of diagnostic procedures (laboratory, instrumental tests, etc.) should be documented and/or attached to the CRF.

The investigator must monitor SAE for the entire study duration (including the follow-up period) until the outcome.

The investigator must monitor cases of pregnancies that occurred while on treatment with the investigated treatment or during follow-up period and document any congenital abnormalities.

Reporting requirements

The investigator must report SAEs (both related and unrelated to the investigated product) by faxing the CRF Adverse Event Form pages **no later than 24 hours** after he/she became aware of the SAE:

If safety issues are dealt with directly by Sponsor:

Sponsor medical expert O.N. Tkacheva,

tel. +7(495)210-73-27, mob. +7(985)211-85-23

tkacheva@rambler.ru

All serious adverse events must be monitored until the outcome.

Any information and required documents that may be available (copies of results of laboratory tests, procedures, autopsy, cause of death data, etc.) will be provided by the Investigator by means of separate written reports directly to the Sponsor medical expert as soon as possible.

The investigator should comply with applicable local regulations for AR reporting to regulatory authorities/ethics committees.

Safety Reporting to Abbott.

(a) Institution and Investigator shall comply with all applicable regulations with respect to the documentation, assessment, and reporting of safety data, including but not limited to the submission of expedited and periodic reports to the appropriate regulatory authorities and Ethics Committees.

(b) In addition, in an effort to assist Abbott with its obligation to collect world-wide safety information with respect to the Study Product(s), Institution and Investigator shall report to Abbott:

(i) all periodic reports regarding the Study contemporaneously with corresponding submissions to authority(ies);

(ii) any safety issues related to the Study;

(iii) any safety signal associated with the Abbott Product(s);

(iv) interim Study reports, if applicable; and

(v) the final Study report and/or or the corresponding publication addressing safety data and findings.

(c) The above mentioned safety information and reports shall be provided by Institution or Investigator to Abbott's Pharmacovigilance department.

(d) Abbott is obliged to provide Institution and/or Investigator with the current information on the safety and efficacy of the Study Material as described in the most current version of the Summary of Product Characteristics.

(e) The parties agree to exchange certain safety related information with respect to the Study Materials without delay, including but not limited to new risks, safety variations, any regulatory action based on safety reasons, or any voluntary activity by the parties due to safety reasons.

(f) Failure of Institution or Investigator to transmit such reports and/or information as mentioned above in a timely manner may result in withholding of further shipment of Study Materials and/or withholding of Study funding.

(g) All Pharmacovigilance-relevant information mentioned above relating to the Abbott Product(s) shall be reported to the following contact:

- Alexey Ryakhin, MD, Pharmacovigilance Manager / ASR

Abbott Laboratories LLC 125171, Moscow, Russia 16a Leningradskoe Highway, Building 1, floor 6.

Tel:+7(495) 258-42-80 ext. 57478

Fax:+7(495) 258-42-81

Mobile/Cell: +7 (926) 101-49-64

e-mail : aleksey.riahin@abbott.com

- Anton Pisarikhin, Pharmacovigilance Specialist / ASR back-up

Abbott Laboratories LLC 125171, Moscow, Russia 16a Leningradskoe Highway, Building 1, floor 6.
Tel:+7(495) 258-42-80 ext. 57478
Fax:+7(495) 258-42-81
Mobile/Cell: +7 (926) 197-99-66
e-mail : anton.pisarihin@abbott.com

8.5 Sponsor responsibilities for AE reporting

The sponsor should ensure that all necessary information about suspected serious and suspected unexpected serious adverse reactions (SUSAR) is duly reported to the regulatory authorities and to Ethics Committees within the appropriate time period after the sponsor became aware of the event (the day when the Sponsor received a SUSAR report):

- fatal and life-threatening unexpected events - not later than 7 days;

- other unexpected serious events - not later than 15 days.

The sponsor should ensure that in case any further information about the event becomes available, all the required data and supporting documents (which may become available in the future) is also duly reported within the time period specified above.

9 DATA MANAGEMENT AND RECORD-KEEPING

9.1 Data collection and processing

The investigator must fill out Case Report Forms (CRFs) according to the instructions obtained before the start of the study. Paper CRF will be used in the study. The investigator must store a copy of a CRF along with other study documents in a place with restricted access. All data documented in CRFs must be supported by the data in the patient source documents.

CRF data will be entered into the integrated database by authorized personnel in accordance with internal Sponsor SOPs. Double data entry will be employed. All data will be systematically analyzed for errors and inaccuracies. Data that need clarification is entered into special forms and sent to the site for clarification. After questionable data is clarified, copies of the signed forms must be stored in the CRF and the originals must be provided to the data managing staff.

The database will be locked after all questionable data are verified, and it is confirmed that the entered data are complete and accurate.

Statistical analysis will be conducted under the supervision of a responsible biostatistician according to prespecified statistical analysis plan (please refer to “Statistical analysis”).

9.2 Data recording

The investigator is required to maintain source documents for every study participant, containing demographic and medical data, including results of protocol-specified investigations. All information contained in CRFs should match the source documents. The investigator must fill out a CRF based on patient's medical record and should store the study documents, including informed consent form, the protocol, the investigator's brochure, and all protocol amendments in a room with restricted access.

9.3 Archiving

The investigator must ensure appropriate documentation storage for at least 15 years after the end of the study. Disposal of the study documents is possible with the Sponsor written permission. The sponsor should inform the investigator in writing about the expiration of the documentation storage term.

Key documents (that allow evaluating the study conduct and quality of the data obtained) should be stored in a way that ensures their integrity and complete security for the entire storage term, and also guaranties their availability on request from competent authorities.

The key documents include:

- Written approval of the study protocol with all amendments by Ethic Committee
- All source documents and results of investigations
- Patient informed consent forms (with protocol number and study name)
- Any other documentation relevant to the study.

10 STATISTICS

Statistical Analysis

10.1 General methods of analysis

Statistical analysis will be conducted under the supervision of a responsible biostatistician. The details of statistical analysis will be provided in the statistical analysis plan in accordance with the GCP requirements and other relevant requirements and laws. The statistical analysis plan will be finalized before the data lock point. All deviations from the final statistical plan version will be justified in the final program report.

The results will be combined for the complete study sample. Two-sided levels of significance and confidence intervals will be calculated. The significance of differences will be calculated for two-sided tests, with a critical significance level of 0.05.

For parameters of interval scale type, the following will be calculated: the arithmetic mean (95% confidence interval for the mean), standard deviation, median, 25th and 75th percentiles. For parameters of ordinal scale type, median, 25th and 75th percentiles will be calculated. For parameters of nominal scale type, frequency categories and confidence intervals for the frequencies (modified Wald method) will be calculated. If the assumptions made during the preliminary study planning are found to be erroneous, the analysis methods will be modified to conduct a more suitable analysis. The result of the primary endpoint analysis will be presented as an absolute number and proportion (%) of patients with target BP (<140/90 mm Hg) achieved at visit V4.

Statistical analysis will be carried out using SPSS/PASW Statistics software package (version 18), SPSS Inc., Chicago, Illinois, USA.

10.2 Procedures for accounting for missing, unanalyzable and questionable data

In case of missing, unanalyzable and questionable data appropriate statistical methods will be applied. Patients who did not complete the planned treatment course will be added to the analysis by the last observation carried forward method.

Patient population for statistical analysis

The following patient populations will be used for the statistical analysis:

Intention-to-treat population (ITT): all enrolled patients with investigations data from visits V3 or V4, excluding the enrollment visit.

Per protocol patient population (PP): patients who completed the study according to the protocol.

Analysis of demographics, disease data, concomitant therapy, and other baseline data

Demographic data (age, gender), the initial condition data (height, weight, body mass index) will be presented along with a summary in the form of a rate or percentage, or by using the mean, standard deviation, median, interquartile range, minimum and maximum, depending on the type of the variable.

10.3 Efficacy Analysis

Efficiency analysis will be carried out in the population of patients who completed the study according to the protocol (PP).

The main indicator of the treatment efficiency:

Changes in mean values of the bone resorption marker (collagen type 1 C-telopeptide) at the end of the study (V4) from the baseline (V1) in comparison between the groups.

Secondary efficiency indicators:

- Changes in mean values of telomerase at the end of the study (V4) from the baseline (V1).
- Changes in mean values of Hs-CRP, lipids, PWV and IMT at the end of the study (V4) from the baseline (V1).
- Changes in mean values of the bone synthesis and resorption markers (osteocalcin, collagen type 1 C-telopeptide) at the end of the study (V4) from the baseline (V1).
- Changes in mean values of the bone synthesis marker (osteocalcin) at the end of the study (V4) from the baseline (V1).
- Changes in mean values of the receptor activator of nuclear factor kappa-B ligand (RANKL) at the end of the study (V4) from the baseline (V1).
- Changes in mean values of BMD at the end of the study (V4) from the baseline (V1).

- Proportion of the treatment responders (defined as the proportion (%) of patients who achieved target blood pressure <140/90 mmHg) after 8, 24 and 48 weeks of the investigated treatment (V2, V3 and V4).

The treatment efficacy will be evaluated on visits V2, V3 and V4 based on SBP and DBP measurements. Clinical response to the treatment is defined as follows:

- Responders: hypertension control, if BP <140/90 mmHg at the visit.
- Non-responders: uncontrolled hypertension, if BP ≥140/90 mmHg at the visit.

The efficacy results will be presented using descriptive statistics. Historical control (publications data) will be used to interpret the results.

10.4 Safety analysis

All safety data will be analyzed in the safety analysis population. Safety analysis includes identification of all adverse events, including serious adverse events at every visit following the screening.

Analysis of adverse events including serious adverse events will be conducted to determine the total number of AEs, the total number of patients with adverse events, the number of treatment-related adverse events, the number of AEs associated with product discontinuation and the number of voluntary withdrawal of informed consent.

Rate and severity of all adverse events and drug-related adverse events (i.e., at least "possibly" associated with the studied product) will be summarized by organ systems. Data on the product withdrawal due to adverse events will be summarized in tables. The safety results will be presented using descriptive statistics.

Interim Analysis

No interim analysis will be performed for this study.

10.5 Sample size rationale

As this is an explorative study with open design no formal sample size calculation was performed. The focus of the study is to obtain scientific data for a publication and taking into account a reason of feasibility of enrollment to timelines and screening of 300 patients per year in assumption that ratio of screened / enrolled patients is approximately 3 to 1 so it is expected that not less than 100 patients but no more than 114 patients will be enrolled in the study. According to this approach the total sample size is chosen 114 subjects.

.10.6 Direct access to source data/documents

The investigator must provide direct access to source data and source documents to CRAs and other sponsor representatives, auditors, Ethics Committees and regulatory authorities representatives.

11 QUALITY CONTROL AND ASSURANCE

This study will be conducted in compliance with the principles and requirements specified in the following documents:

- Declaration of Helsinki regarding medical research on humans (recommendations for physicians on biomedical research involving human subjects, Helsinki 1964, amendments Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000, Washington 2002, Tokyo 2004, Seoul 2008).

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996,

and in accordance with local regulatory requirements.

By signing the protocol, the investigator agrees to comply with the instructions and procedures described in the protocol and, thereby, to comply with the principles of Good Clinical Practice followed by the protocol. A copy of the Declaration of Helsinki will be kept in the investigator's folder in every study site.

Audit, inspection

In order to ensure compliance of the study with GCP and regulatory requirements, the study may be audited by external organizations, or regulatory authorities, in addition to sponsor monitoring. In the case of audit/inspection, the investigator must provide the auditors with access to any study related documents.

12 ADMINISTRATIVE ISSUE

12.1 Changes to the study protocol

Any protocol changes are made in the form of a written amendment which must be signed by Sponsor and investigator before it comes into effect. For amendments affecting

subject's security, study objectives or scientific content, additional approval by Ethics Committees is required.

Changes affecting only administrative aspects of the study (addresses, phone numbers, minor changes in the investigated product packaging) do not require formal registration as an amendment or Ethics Committees approval, but these organizations are informed about the administrative changes.

12.2 Early study termination

Early termination of the study and/or a study site may occur by Sponsor or the investigator decision as well as at the regulatory authorities' request.

In case of early study site closure or study termination, all filled out and unused CRFs and other documents (except for documentation that must be kept in the center) to be transferred to the Sponsor. The study materials may be disposed of at the site only with Sponsor's permission.

Principal Investigator should promptly inform investigators and regulatory authorities about early study or site termination specifying the reason for termination.

12.3 Final report

The final study report will be prepared by PI / sponsor within 5 months after the data lock point. The report will be prepared whether the study in terminated early or completed as planned. The report is signed by Principal Investigator.

13 ETHICAL AND REGULATORY ASPECTS

13.1 Ethics committee

Prior to the study initiation, the protocol and related documents (including CRFs and patient information materials) must receive approval by Independent Ethics Committees in writing. All protocol amendments also must be approved.

The study may not be initiated in any site before the written permission from Ethics Committee(s) is obtained, relevant local legislation requirements are met, and the clinical trial protocol is signed by all involved parties.

13.2 Informed consent

The investigator (or his/her authorized representative) must obtain a written consent of every patient to participate in the study prior to any study procedures may be performed. Before that, the investigator (or his/her authorized representative) should inform the patient about the purpose, benefits, risks and requirements of the study, and about the nature of the investigated products.

The patient will be provided with information about the study (Patient information booklet) and the informed consent form to participate in the study, set out in plain language. A patient must be given enough time to ask questions about the details of the study and to make a decision about participation in the study.

Two originals of Patient information booklet and informed consent form to participate in the study must be filled out dated and signed by the patient and the person responsible for obtaining the informed consent.

If the patient is unable to read the document, an unbiased witness must be present during the entire period of the informed consent discussion. The patient must orally agree to participate in the study and also fill out, sign and date the Patient information booklet and the informed consent form, if she can do it. Then, the witness and the person responsible for obtaining the informed consent must fill out, sign and date this form as well.

Signed Patient information booklet and informed consent form is given to the patient, the other two signed originals will be stored by the investigator.

Patient information booklet and Informed consent form are a part of the protocol and will be submitted to the Ethics Committee for approval. If new information that may be important for subject's consent to participate in the study becomes available, it will be reflected in a new version of the Patient information booklet and Informed consent form approved by the Ethic Committee; the new versions of the documents must be signed and dated by patients.

13.3 Regulatory authorities

Before the start of the study, regulatory approval to conduct this study will be obtained in every participating country. List of investigators and study sites will be approved.

13.4 Confidentiality

All documents and information provided by the investigator to the sponsor relating to this study are strictly confidential.

The investigator and his/her staff take responsibility to use these data only to conduct the study according to the protocol. This agreement remains in force until the confidential information is disclosed by the sponsor. Work study protocol provided to the investigator may be used by the investigator or his/her staff to obtain patient's informed consent to participate in the study. The content of the protocol may not be disclosed to others without written permission form the sponsor.

The investigator must fill out and keep a patient screening log and an identification list of all enrolled patients; the investigator should content to grant access to the site for auditors and/or regulatory authorities representatives. Handling of the information will meet the requirements of professional secrecy. Patient screening log should be filled out every time the investigator evaluates a patient for possible enrollment to the study (by evaluating patient history during a visit or assessing patient medical records).

The investigator and Sponsor must ensure the protection of personal data of study subjects according to applicable local regulations. Required personal data of study subjects (eg, socio-demographic characteristics) will be collected solely for the purposes of the study with minimal required details. CRFs will not contain patient names, addresses, or numbers of medical records/charts. No documents identifying the patients will be disclosed. Sponsor and CRO will not be provided with patients' first or last names. If a patient's name is mentioned in any document, the patient's name must be deleted from the document before transferring it to Sponsor.

Prior to enrollment in the study, patients will be familiarized with conditions of confidentiality and their personal data use, including requirement to access the data by CRAs and other authorized persons (in the case of audit, inspection, etc.). These conditions will be reflected in the Patient information booklet. The patient is enrolled into the program only after reading the above information and signing the Informed consent form.

14 PATIENT INSURANCE

Sponsor provides life and health insurance of patients participating in this study.

15 PUBLICATIONS

The study sponsor assumes full responsibility arising from this function, and retains exclusive ownership of all the results obtained in the present study, which it can use at its own discretion. Publication of study results is prohibited without the Sponsor permission. Results

will be published in a peer-reviewed journal following ICJME guidelines with following publication in Russian language The final study report and a resulting publication will be provided to Abbott upon their approval/availability. Prior to any publishing, Abbott approval of the study report and the manuscript(s) for publication is required and will be ensured.

Publication of study results is subject to ethical principles. The publication authors must guarantee accuracy of the data, regardless of whether the data are positive or negative.

On the part of the Sponsor, every effort will be made to publish the results of the study; the Sponsor ensures that the data will be provided in a reliable and clear way.

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17. Рекомендации по лечению артериальной гипертонии. ESH/ESC 2013

17 APPENDICES

17.1 Appendix 1 Blood pressure and heart rate measurement

Systolic and diastolic blood pressure and heart rate will be measured at every visit according to ESH/ESC recommendations [17]. Blood pressure and heart rate is measured on patient's arms.

Position of the patient:

Sitting in a comfortable position; the arm is on the table, at the heart level; sphygmomanometer cuff is placed around the upper arm, the cuff lower end should be 2 cm above the elbow.

Blood pressure measurement conditions:

- coffee and strong tea should be avoided within 1 hour prior to the measurement;
- it is recommended to avoid smoking for 30 minutes before the measurement;
- sympathomimetics, including nasal and eye drops, are withheld;
- Blood pressure is measured after 5 minutes of resting; if the BP measurement procedure was preceded by significant physical or emotional stress, the resting period should be extended to 15-30 minutes.

Equipment:

- the cuff size should match the size of patient's arm: inflatable rubber portion of the cuff should cover at least 80% of the arm circumference; 12-13 cm wide and 30-35 cm long cuff is used for adults (medium size); large and small cuffs for thick and thin arms should be available, respectively;
- before the measurement, sphygmomanometer pointer should point at zero.

Number of measurement:

- **at least two measurements at an interval of at least 1 minute** should be made to evaluate BP; at the screening and enrollment visits, BP should be measured **3 times at an interval of at least 1 minute.**
- if the difference between measurements is >5 mmHg, an extra measurement is done; an average of the last two measurements is documented;

Measurement technique:

- rapidly inflate the cuff to pressure 20 mmHg higher than SBP (disappearance of the pulse);
- BP is measured with 2 mmHg accuracy;
- the cuff pressure should be reduced at a rate of about 2 mmHg per second;
- the pressure at which first tone is heard corresponds to SBP (first Korotkoff sound);
- the pressure at which the tones are no longer heard (fifth Korotkoff sound) corresponds to DBP. If the 5th sound cannot be determined, one should try to identify 4the Korotkoff sound which is characterized by a significant weakening of the tones;
- if the tones are very weak, the patient should raise her arm and make a fist a few times, then the measurement should be repeated; the stethoscope membrane should not compress the artery too hard;
- at the initial patient's physical examination (at screening), blood pressure should be measured on both arms; later the measurements are done on the arm with the higher pressure;
- heart rate is calculated based on radial pulse (counted for at least 30 seconds) after the last blood pressure measurement in the sitting position.

17.2 Appendix 2 Classifications of hypertension and heart failure severity

1. Hypertension severity according to ESH/ESC recommendations:

BP categories	**SBP**		**DBP**
Optimal	< 120	and	< 80
Normal	120 - 129	and/or	80 - 84
High normal	130 - 139	and/or	85 - 89
- Hypertension Grade 1	140 - 159	and/or	90 - 99
- Hypertension Grade 2	160 - 179	and/or	100 - 109
- Hypertension Grade 3	≥ 180	and/or	≥ 110
Isolated systolic hypertension *	≥ 140	and	< 90

Note: *Isolated systolic hypertension should be classified as grade 1, 2, 3 based on SBP.

If systolic blood pressure (SBP) and diastolic blood pressure (DBP) values fall into different grades, the hypertension severity is estimated based on the higher grade. Most accurate determination of hypertension grade is possible in patients with newly diagnosed hypertension, and in patients not taking antihypertensive medications.

17.3 Appendix 3 Diet recommendations

According to ESH/ESC 2013 Guidelines for the management of arterial hypertension patients should be advised to eat

- vegetables,
- low-fat dairy products,
- dietary and soluble fibre,
- whole grains and
- protein from plant sources,
- reduced in saturated fat and cholesterol.

Fresh fruits are also recommended — although with caution in overweight patients because their sometimes high carbohydrate content may promote weight gain.

Patients with hypertension should be advised to eat fish at least twice a week and 300–400 g/day of fruit and vegetables. Soy milk appeared to lower BP when compared with skimmed cows'milk.

Patient number: _____

Patient Information Sheet

Title: COMPARATIVE EFFECTS OF MOXONIDINE AND BISOPROLOL ON BONE METABOLISM, VASCULAR AND CELLULAR MARKERS OF AGING, BLOOD PRESSURE IN HYPERTENSIVE POSTMENOPAUSAL WOMEN

Principal Investigator/Sponsor: O.N. Tkacheva, Professor, Dr.Med.Sci.

Institution/Study site: Federal State Budgetary Institution "State Scientific and Research Center of Prophylactic Medicine" of the Ministry of Healthcare of the Russian Federation (FSBI "SSRCPM" of MoH of Russia).

Dear Patient!

You have been asked to participate in a scientific and research program conducted under guidance of Professor, Dr. of Medical Sciences, Olga Nikolaevna Tkacheva.

Before you agree to participate in the program, you have to get information about goals and content of the program, investigational products, possible risks and benefits in order to take a grounded decision. Such procedure is called "informed consent".

This document may contain words you do not understand. Please ask the investigator doctor or a investigator team member to explain you meaning of such words or any information that is not clear for you. You may keep unsigned copy of this document and think or discuss it with your family members or friends before you make a final decision.

After you read information about the conducted program and all planned procedures that you will have to undergo, you will be asked to sign this form to be able to participate in the program. Your decision about participation in this program is voluntary: it means that you are free to decide whether to participate in it or not. You may also freely leave the program at any time without explanation of reasons. If you decide not to participate in this program, you may discuss with the study doctor standard treatment of your disease.

General information about the program and its objective

In this scientific program influence of the drug product Moxonidine (Physiotens) on bone metabolism and vascular parameters of aging are being studied.

It is well-known that cardiovascular diseases (CVD) associated with atherosclerosis are general reasons of disease incidence, invalidity and mortality in developed countries, and according to the WHO evaluations, they threaten to become the main reason of mortality in developing countries too within the next decade. One of the reasons of such dramatic growth in number of heart attacks, blood strokes, heart failures is constant aging of population. The more the aging

changes in a vascular wall are expressed, the easier and quicker atherosclerosis, arterial hypertension and other pathologic processes develop, that in their turn accelerate aging changes. Postmenopause is a period in a woman's life characterizing by acceleration of aging processes, increasing incidence of arterial hypertension, progressiving insulin resistance. Positive influence of Moxonidine on insulin resistance detected in previously conducted clinical studies allows viewing it as a prospective antihypertensive agent with potential influence on cellular and vascular aging.

Osteoporosis is one of the frontmost problems of women's health in line with development of arterial hypertension. Among all the existing forms of osteoporosis postmenopausal osteoporosis takes about 85%. Bone metabolism is shifted to increased resorption with aging, that leads to osteopenia or to osteoporosis in people with predisposition to quick bone mass loss. Bone strength depends on the amount of bone mass and quality of bone tissue. Results of experimental studies showed ability of Moxonidine to inhibit processes of bone resorption by means of influencing on activity of osteoclasts. It was also observed in experimental studies that Moxonidine may slow down bone mass loss in laboratory animals, that is a prerequisite for clinical examination of Moxonidine influence on bone tissue density.

This study is a complex examination of Moxonidine influence on processes of cellular, vascular aging, bone metabolism.

The drug is officially registered for use in Russia, one of registered indications is arterial hypertension.

Based on information received during examination of the drug it is expected that results of the study will help to optimize approaches to treatment of female patients with arterial hypertension and concurrent osteopenia during postmenopause, and to receive additional information about connection between progression of bone resorption and increased stiffness of arterial wall.

In this program it is planned to examine influence of Moxonidine compared to bisoprolol on bone metabolism and bone tissue density in postmenopausal women with hypertension and osteopenia.

It is planned to enroll postmenopausal patients with arterial hypertension and osteopenic syndrome.

114 postmenopausal patients with arterial hypertension and osteopenic syndrome will participate in the program.

Enrollment in the program

Your doctor will perform necessary medical examination to determine whether you are able to participate in this scientific program or not.

Examination will include medical history review, physical examination, collection of information about age, gender, etc., evaluation of severity and stage of arterial hypertension in accordance with recommendations of ESH/ESC.

You have to inform your doctor of all known information about your disease, including all the drugs you take (including administration of non-prescription drugs, herbal drugs and biologically

active food supplements) and specify whether you participate or have participated in other studies.

Your doctor will ask you questions about cardiovascular diseases and other significant concurrent diseases and their treatment.

Blood samples will be collected.

Your blood pressure, pulse, height and weight will be measured.

The following procedures will be performed: electrocardiography, X-ray absorptiometry, evaluation of arterial stiffness, evaluation of subclinical atherosclerosis signs.

Program procedures

The program consists of screening period and treatment period. If you fully correspond to the program inclusion criteria and want to participate in it you will receive one of the study drugs – bisoprolol or Moxonidine from the doctor. If at the moment of screening visit you are already taking any drug for hypertension, this drug will be cancelled for 2 weeks. Dosage scheme will be chosen by the doctor in accordance with the specific clinical situation.

Moxonidine will be prescribed by the doctor in accordance with the approved instruction for medical use and within normal clinical practice. Initial dose of Moxonidine will be 0.4 mg daily in the morning. Drug dose is chosen for you personally by the doctor and only the doctor will be able to change it upon his decision depending on the treatment effect. Daily dose of Moxonidine may reach 0.6 mg.

Bisoprolol will be prescribed by the doctor in accordance with the approved instruction for medical use and within normal clinical practice. Initial dose of bisoprolol will amount to 5 mg once daily in the morning. Drug dose is chosen for you personally by the doctor and only the doctor will be able to change it upon his decision depending on the treatment effect. Daily dose of bisoprolol may reach 7.5 mg.

Besides it will be recommended for you to take calcium and vitamin D3 supplements for treatment of osteopenic syndrome, you will have to take 1 tablet daily with food.

At visit 2 that will be performed in 8 weeks since enrollment visit the doctor will perform general medical examination, evaluate symptoms of arterial hypertension and possible adverse events for the preceding period. You will receive study drugs and instructions about dosage and regimen of the drugs administration. Expected duration of the visit is 1.5-2 hours.

Approximately in 14 and 28 days after enrollment visit the doctor will contact you via phone to ask how you feel and whether you had any changes in health since the previous visit.

At visit 3 that will be conducted in 24 weeks after the enrollment visit the doctor will perform general medical examination, ask you questions about concomitant therapy and possible adverse events. Electrocardiography will be performed and blood samples will be collected.

At final visit 4 that will be performed in 48 weeks after the enrollment visit the blood samples will be collected. Your blood pressure, pulse, height and weight will be measured. The following

procedures will be performed: electrocardiography, X-ray absorptiometry, evaluation of arterial stiffness, evaluation of subclinical atherosclerosis signs. Expected duration of visits 3 and 4 is 1.5-2 hours.

Duration of participation

Your participation in this scientific program will start since signing of this consent form and will last approximately 12 months since signing of informed consent form of the Patient Information Sheet.

Termination of participation in the program

You may stop participating in this program at any moment. Also your doctor may take a decision about premature termination of your participation if he considers it necessary. Termination of participation in the program will not influence your right to get treatment or relations with your study doctor. Please inform your study doctor immediately if you want to stop treatment. If you or your doctor decide to stop your participation in this program, you may be asked to come to a study termination visit for final evaluation.

Data we collect from you

During the program information about your health condition from your medical records, all received information about you during your participation in the program will be collected. Your personal information (full name, date of birth, gender) will be used in the form of a digital code for analysis of medical information and for assignment of a patient number to you. Patient number will also be specified on the first page of the both copies of Patient Information Sheet.

How your data will appear

During processing and analysis you will not be identified by your name, address, insurance number, etc. in any databases used outside the medical institution. If study results are published, they will not contain any information that may identify your personality. Information that will be collected about you will be taken from your medical records that are kept at the Federal State Budgetary Institution “State Scientific and Research Center of Prophylactic Medicine” of the Ministry of Healthcare of the Russian Federation (FSBI “SSRCPM” of the MoH or Russia). Your agreement for use of your information by the study personnel starts working after signature of this document and has no term of validity. If you do not provide your agreement for use and transfer of information about your health, you will not be able to participate in this program.

Why we collect this data

Results of performed treatment during your participation in the program may have scientific value. Scientific information received in the course of this program may be used in the program reports and scientific reports. But information that may identify your personality will not be published.

Who will see your data

All medical records will be kept at the premises of the scientific program conduct, at the Federal State Budgetary Institution “State Scientific and Research Center of Prophylactic Medicine” of

the Ministry of Healthcare of the Russian Federation (FSBI "SSRCPM" of the MoH or Russia) by the responsible doctor.

Only your doctor will have access to your personal information and your medical records. Due to this your doctor has to receive your consent for use and processing of your personal data. Your consent for use and processing of your personal data by your doctor starts working after signing this document and has no term of validity. You have a right to disable use and processing of your personal data and medical information collected during the scientific program at any moment without explanation of reasons. In this case you will prematurely terminate your participation in this program but you will not lose any rights for alternative treatment. If you do not provide your consent for use and transfer of your health information you will not be able to participate in this program.

Information about your health will also be available to other doctors that participate in this scientific program, and also to members of ethics committee and regulatory and law enforcement executives.

Processing of your personal information about your health includes but is not limited to collection, analysis, transfer (in any form), use and storage of such information.

Risks/benefits

Moxonidine (Physiotens®) is a prescription drug product approved for use in the Russian Federation, imidazoline receptor I_1 agonist, indicated at arterial hypertension. Prescription and dosage calculation of the drug will be performed in accordance with the approved instruction for use, maximum daily dose may reach 0.6 mg.

Risks connected with administration of Physiotens® may be connected with development of its side effects. It is necessary to note that some adverse events registered during clinical studies sometimes were associated with arterial hypertension symptoms but not with treatment with Physiotens®.

The most frequently registered adverse symptoms are dryness in mouth, dizziness, asthenia and drowsiness. Such symptoms often reduce after the first weeks of treatment.

Less frequently the following events have been registered: faint, expressed lowering of blood pressure, orthostatic hypotension, bradycardia, diarrhea, nausea, vomiting, dyspepsia, skin rash, itching, angioneurotic edema, insomnia, nervousness, tinnitus, back pain, neck pain.

It is necessary to be especially careful at administration of Moxonidine in patients with atrioventricular block I grade (risk of bradycardia development); severe coronary artery disease and unstable angina (experience of administration is insufficient); renal insufficiency.

Overdose

There are reports about several cases of overdose without lethal outcome with one-time administration of dose up to 19.6 mg.

Symptoms: headache, sedative effect, drowsiness, expressed lowering of blood pressure, dizziness, asthenia, bradycardia, dryness in mouth, vomiting, fatigue, epigastric pain, respiratory distress, impairment of consciousness.

Besides the following events are possible: short-term blood pressure increase, tachycardia and hyperglycemia, as it was shown in several studies of high doses on animals.

Unknown risks

Although Physiotens® is registered and is used for treatment of arterial hypertension, you may have side effects or adverse events unknown currently, i.e. not described in approved instruction for medical use. Please inform your doctor immediately if you develop any problems with health.

Other possible treatments

If you decide not to participate in this program, suitable standard treatment will be prescribed to you.

Expenses

Expenses for standard treatment of your condition and routine examination procedures outside this program will be paid by you or your insurance company. The study drug will be provided free of charge and medical examinations necessary for this scientific program conduct will also be performed free of charge.

Compensation

You will not receive any monetary compensation for participation in this program.

Insurance

Additional insurance of patients participating in this program will be provided.

Who may I contact with for additional information?

If you have any questions about this program, please contact the doctor responsible for its conduct: Ekaterina Nailievna Dudinskaya, tel.: +7 499 553 68 91 or +7 903 191 46 90, or Diana Vadimovna Trofimova, tel.: +7 965 126 49 52.

You may get additional information about your rights in the Ethics Committee: +7 499 553 68 91.

Contact information of the Ethics Council of the Ministry of Healthcare and Social Development of the Russian Federation: 3 Rakhmanovsky lane, Moscow, 127994. Tel. +7 495 438-23-88.

Informed Consent Form

I understand what this program suggests. I have read Patient Information Sheet. I have received answers to all my questions. I know that participation in this program is voluntary. I can refuse to participate at any time and will not lose any benefits that I could have got in other case. I received explanations about the character of the study, risks and benefits connected with it, other

possible treatments, procedures and objective of the study. By signing this form I do not lose any of my legal rights.

I understand that my personality will be kept secret, and information collected during this program will be used for scientific purposes and in scientific publications.

I give my consent for regulatory and law-enforcement bodies or their designated employees to access my medical records.

I will be informed of all new information that becomes available to my doctor in the course of this program and that may influence my desire to continue my participation in it. If I want to inform about it my treating physician, I should inform doctor Diana Vadimovna Trofimova, tel. +7 965 126 49 52.

Statement of consent:

By signing below I confirm that I have read this Patient Information Sheet and Informed Consent Form, discussed all details of the program with my doctor, had a chance to ask questions and received satisfactory answers, and I voluntarily agree to participate in this program as specified in this form.

I have received signed and dated original of Patient Information Sheet and this Informed Consent Form.

_____

Full name of a patient, printed

_____

Signature of a patient Date

_____

Full name of a Principal Investigator / authorized Co-Investigator, printed

_____

Signature of a Principal Investigator / authorized Co-Investigator Date