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ABP 051

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APPROVED BY
General Director
FSBI "Almazov National Medical Research Center"
_____ E. V. Shlyakhto
«__» _____ 2019

Clinical study report

Title of the clinical study report	Effect of course administration of the transcutaneous electrostimulator for blood pressure "ABP-051" on circadian blood pressure values
Identification of the study device (including its name, model, etc.)	Transcutaneous electrostimulator for blood pressure correction "ABP-051" per 9444-005-12342964-2015. Manufacturer: "Inferum" LLC (620026, Russia, Sverdlovsk Region, Yekaterinburg, Belinsky Str., 86-487).
Study period	27.02.2019 – 15.07.2019
Report number	№ 786
Версия отчета	1.0
Study sponsor	Under agreement №48 between customer "Schwabe-Moscow" LLC and Federal State Budgetary Institution "Almazov National Medical Research Center", Russia, 197341, Saint-Petersburg, Akkuratov Str., 2.
Study program (plan)	№786
Study site	Federal State Budgetary Institution "Almazov National Medical Research Center", Russia, 197341, Saint Petersburg, Akkuratov Str., 2. The study was carried out in outpatient settings on the base of the research laboratory of circulation physiology.
Study coordinator	Deputy in scientific work of FSBI "Almazov National Medical Research Center" A.O. Konradi
Compliance statement	The study was carried out in accordance with GOST R ISO 14155-2014 requirements (identical to ISO 14155:2011)
Protocol author	Research associate of the research laboratory of circulation physiology, Cand. Med. Sc. O.V. Mamontov.
Report location and date	03.10.2019, Saint Petersburg

SYNOPSIS

Title of the clinical study: effect of course administration of transcutaneous electrostimulator for blood pressure correction “ABP-051” on circadian blood pressure values.

Nowadays, medicinal products form the basis of essential hypertension (EH) therapy. Stimulator “ABP-051” allows to influence blood pressure (BP) level using non-drug method, however, its efficacy has been only checked by comparison of individual BP measurements.

***Study goal*:** to assess effect of course administration of stimulator “ABP-051” on circadian BP values reconstruction based on three-day monitoring in hypertonic patients.

***Patients*:** 62 patients with I-III grade essential hypertension: untreated patients with I grade EH and patients with II-III grade EH having regular stable therapy randomized to 2 groups were enrolled to the study: treatment group of 52 subjects being stimulated by device ”ABP – 051” and 10 subjects having sham stimulation with the active model simulator.

***Examination methods*:** dynamics of BP level and profile was investigated in all patients during the dynamic assessment based on reconstruction of three-day BP monitoring using the method of non-sinusoidal variance, as well, its dynamics was assessed immediately during the stimulation using method of continuous non-invasive BP measurement.

***Results*:** it has been established that stimulation therapy being administered once is not accompanied with adverse effects and does not lead to significant BP variations. During course therapy, a significant decrease of BP level and circadian values was observed in 66% of patients. The effect of course administration was observed to the end of 2-week stimulation cycle, it maintained in most patients during 2 weeks after its completion. In general, one or another positive effect on circadian values was observed in 90% of patients.

Conclusion: course administration of “ABP–051” is safe, it promotes improvement of circadian BP values in 90% of hypertonic patients.

INTRODUCTION

Effect of course administration of transcutaneous electrostimulator for blood pressure correction “ABP-051” on circadian blood pressure values

Essential hypertension is the most important risk factor of cardiovascular mortality in most developed countries including Russian Federation, however, adequate disease treatment improves prognosis in patients with the disease. Nowadays, medicinal products administered in various combinations to achieve target blood pressure values for preventing of target organ disorders form the treatment basis. Additional exposures to normalize life style and treat associated conditions are also of great importance in control of the disease progression.

Recently, apparatus approaches for BP correction based on activation of arterial baroreceptors have been developed in Europe and the USA for treatment of essential hypertension. However, due to high equipment cost, the method has not been widely used.

Stimulator “ABP-051” is the continued development of some methods of non-drug correction of essential hypertension based on stimulation of peripheral structures which are supposed to influence cardiovascular center activity leading to BP decrease. The accurate mechanism of effect is not well-known, one of the possible methods for implementing electrostimulation effect is electric impulse exposure to the area located in the internal left wrist.

Efficacy of the device for BP decrease has been earlier shown. However, methodological particularities of the studies did not allow to assess dynamics of 24-hour BP profile in detail as they were based on individual BP measurements and 24-hour BP monitoring.

The present study differs by the fact that operator-independent method based on three-day BP monitoring in series of paired examinations was chosen as the method of efficacy assessment.

The monitoring with subsequent reconstruction of circadian BP profile using the method of non-sinusoidal variance was performed in patients of the treatment group being stimulated with device “ABP-051” and in the control group having sham stimulation. Therefore, the double-blind placebo-controlled study was performed to assess efficacy of the tested equipment by the objective diagnostic method.

1. STUDY DEVICE AND METHODS

1.1 DESCRIPTION OF THE STUDY DEVICE

Model: "Transcutaneous electrostimulator for blood pressure correction "ABP-051" per TU-9444-005-12342964-2015".

Device classification:

Class of the potential risk of the medical device in accordance with the nomenclature classification of medical devices: **2a** (in accordance with Order of MoH RF № 4n dated 06.06.2012, clause 9.4).

Type of the medical device in accordance with the nomenclature classification of medical devices: **181480** in accordance with Order of MoH RF dated 06.06.2012 № 4n "On approval of the nomenclature classification of medical devices".

Code of the All-Russian Classifier of Products for the medical device: **94 4410**

Chemical description.

MD is manufactured in accordance with TU-9444-005-12342964-2015. The device does not contain drug substances, organic tissues or blood products. Being used, the device has short-term contact with a human body. Materials contacting directly with a human body are tested for biological compatibility in accordance with series of ISO 10993 standards, namely materials of the following composition:

- device body is produced from two-colored plastics: grey and dark grey: acrylonitrile butadiene styrene HI 121, by company "LG Chem, LTD" (South Korea);
- electrodes – device contacts are produced from steel 12X18H10T per GOST 5632;
- elastic band (cuff) is produced from polyamide (nylon) brand PA66 by company "CHICO TEXTILE IND. CO., LTD" (China).

Conditions of use

Temperature + 10°C to + 35°C, relative humidity 30% to 93%, atmospheric pressure 70 kPa to 106 kPa. If the device has been kept in environmental temperature below 10°C, it should be kept in normal climatic conditions (room temperature) for at least 12 hours prior the use.

Main technical characteristics

Transcutaneous electrostimulator for blood pressure correction "ABP-051" per TU 9444-005-12342964-2015 has the following characteristics:

- dimensions - (70x71.5x31.5) ±0.5mm;
- device weight with the cuff and in-built electrodes (without power supply cells) - 0.072±0.005kg;
- power consumption – not over 200 mA;
- power supply - 3±0.6 V;
- supply source – galvanic batteries type AAA, 2 pcs.;
- body protection level - IP41.

Device construction and appearance

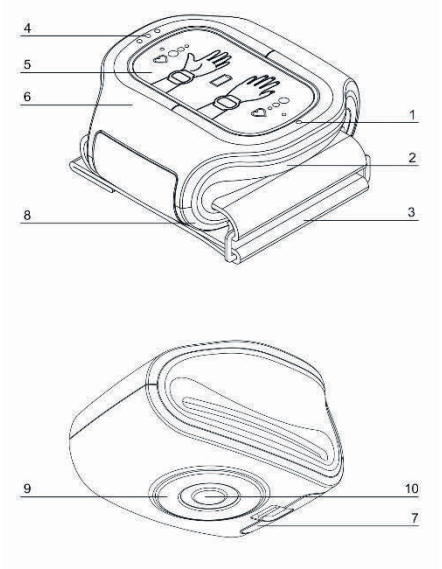


Figure 1. Transcutaneous electrostimulator for blood pressure correction “ABP-051”.

1. On/Off key of the program for correction of decreased blood pressure. 2. Body. 3. Cuff. 4. On/Off key of the program for correction of increased blood pressure. 5. Screen. 6. Body panel. 7. Battery compartment lid. 8. Lower body lid. 9. Electrode 1. 10. Electrode 2.

Therapeutic indications of the device:

- increased blood pressure in hypertonic patients as an adjunct to complex drug therapy;
- circadian blood pressure disorder;
- marked blood pressure fluctuations in hypotonic patients as an adjunct to complex drug therapy.

Device contraindications

Absolute:

- individual intolerability of the electric current;
- presence of an implanted pacemaker.

Relative:

- neoplasms (tumors) of any etiology and location
- acute fevers of unknown origin;
- venous thrombosis;
- acute psychotic, alcohol or drug-induced excitation.

Possible adverse effects

Possible adverse actions of the medical device are not identified.

Determination of the environment for the medical device

Electrostimulator “ABP-051” is intended for health facilities and individual use by patients in home settings for therapeutic exposure. The device is non-sterile.

Determination of patient group

”Transcutaneous electrostimulator for blood pressure correction “ABP-051” per TU 9444-005-

12342964-2015” is intended for therapeutic non-invasive course exposure for correction of blood pressure and normalization of general body condition.

The device is intended for subjects above 14 years with labile essential hypertension and patients with persistent increase of blood pressure as an additional exposure during drug therapy and hypotonic patients as an adjunct to complex drug therapy.

Determination of the administration and technique method

Transcutaneous electrostimulator for blood pressure correction “ABP-051” per TU 9444-005-12342964-2015 is used for a direct short-term with a patient’s skin on the left wrist.

Principle of the device work

Transcutaneous electrostimulation – the method of physiotherapeutic treatment which is based on short low frequency current impulses on human biologically active zones:

- exposure to zone MC6 (Figc.2 - A) is used for blood pressure reduction,
- exposure to zone TE5 (Fig.2 - B) is used for blood pressure increase.

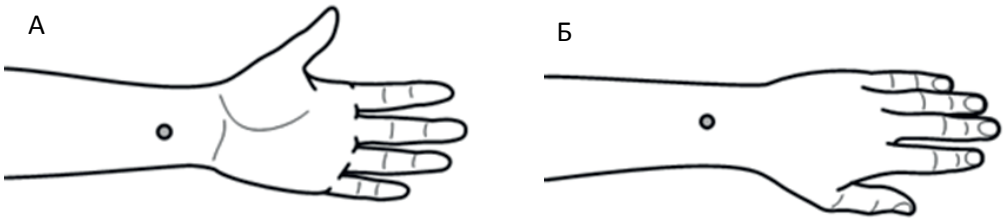


Figure 2 Location of zones MC 6 (A) and TE 5 (Б)

The exposure occurs when the devices touches a patient’s skin through in-built electrodes.

Method of the device administration:

1. to start working with the electrostimulator, measure your blood pressure with the tonometer, then free the left wrist from watch, bracelet and clothes and, put on the device to the arm depending on the exposure area avoiding empty areas between the cuff and wrist, and a close contact is maintained between the device electrodes and skin closely but so that the wrist is not tightened over.

2. Fix the device on the arm in the zone in accordance with the instruction for the use and press button “On/Off”.

3. The device will start exposing to the selected zone; the treatment procedure consists of several exposure phases differing by frequency, time and exposure magnitude, after the session, a sound signal will be heard, and the device will switch off.

4. Take off the device, rest for 20-30 minutes is recommended after the session.

5. To achieve a consistent result, course treatment of at least 14 procedures, 2-3 procedures a day, is recommended.

Procedure for course administration.

After 2 week course of stimulation, 2-week break with subsequently continued stimulation cycle is recommended.

Identified risks

- Do not use the device for children below 14 years.
- Prior the use, please review the information in the operation manual related to safe use, as well recommendations on the correct use and device maintenance.
- Protection level of working parts from electric current GOST R 50267.0 – type BF.
- To avoid the device malfunction, you should not use the device and another electric equipment concurrently.
- The device contains fragile elements, protect it from shocks.
- The device is not water-proof, protect from moisture penetration.
- Keep the device away from heating devices, avoid long-term exposure of direct sunlight in high ambient temperature (over 25°C).
- The device should be operated by a person being awake, adequately perceiving environmental factors. The device should not be used by subjects having threshold mental or inadequate psychiatric conditions.
- Shipment conditions: temperature - 50°C to + 50°C, relative air humidity 30% - 93%, atmospheric pressure 70 kPa-106 kPa, the device should be shipped only in closed vehicles
- Operation conditions: temperature + 10°C - 35°C, relative air humidity 30% - 93%, atmospheric pressure 70 kPa - 106 kPa. If the device has been kept in ambient temperature below 10°C, let it stand in normal climatic conditions for at least 12 hours prior the use.

<u>Determination of potential risk of MD</u>

The manufacturer has submitted the risk analysis report for medical device “Transcutaneous electrostimulator for blood pressure correction “ABP-051” per TU 9444-005-12342964-2015”.
Potential risk was assessed in accordance with:

- GOST ISO 14971-2011 Medical devices. Application of risk management to medical devices;
- GOST IEC 60601-1-1-2011 Medical electrical equipment. Part 1-1. General requirements for safety. Safety requirements for medical electrical systems;
- GOST 24297-2013 Verification of purchased product. Organization and methods of control.

During the risk analysis of the device, potential hazards which can occur on all phases of product life cycle were reviewed, the following risk were identified and reviewed:

• non-compliance of output parameters with required values (deviation of magnitude, impulse frequency, not operating function of load presence/absence);
• misuse of the device in electrostimulation mode;

• non-compliance of the parameters with the intended use;
• malfunction of other devices;
• user damage by electric current in electrostimulation mode;
• infection of a patient, use and third parties;
• chemical environmental pollution;
• use of the device in an incorrect mode (error of work regime indication).

Probability of hazards and severity of consequences of each hazard were assessed. Based on the analysis results, the protective measures were enlisted for decrease of identified risks to the appropriate level, as well references on documents confirming the protective measures. When measures were taken to decrease risk level, new risks were not identified.

Based on the risk analysis, the conclusion was made that the device benefit was greater than residual risk of the device use.

To investigate adverse events related to electrostimulators on the Russian and European market, the search was performed in database MAUDE (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm), MHRA (http://www.mhra.gov.uk) and on the site of the Federal Service for Surveillance in Healthcare from 27.02.2019 to 15.07.2019. The search was made by inquiries: transcutaneuos electrostimulation; TENS; transcutaneous peripheral nerve electrostimulation; dynamic electrostimulation; DENS; electrostimulation. The search of adverse events related to such devices did not show additional risks.

Certification

- Marketing authorization issued by the Federal Service over Surveillance in Healthcare, № RZN 2016/3776 dated March 31, 2016.
- European Certificate of Conformity in accordance with Directive 93/42/EEC for medical devices № 1942/MDD dated 01.09.2017.

1.2 CLINICAL STUDY PLAN

a) Study goal:

To assess effect of course administration of stimulator “ABP-051” on circadian BP values reconstructed on the data of three-day monitoring in hypertonic.

b) Aims of the medical testing:

- To assess efficacy of BP correction based on results of three-day monitoring with outpatient use of device “ABP-051” by patients with II-III grade essential hypertension taking stable therapy or patients with I grade essential hypertension not having any treatment.
- To establish effect of course stimulation with device “ABP-051” on daily profile values: mean 24-hour blood pressure level, time index (TI), BP variability and circadian index (degree of nocturnal BP decrease) based on the paired three-day BP monitoring and further reconstruction of circadian profile using the method of non-sinusoidal variability [G.S. Katinas, M.V. Dementyev, F. Halberg, et.al. Evaluating the form of nonsinusoidal variations // World Health Journal. 2011. 3(2). P. 135—149.].
- To determine consistency of effect on circadian profile in 2 weeks after course device exposure based on three-day BP monitoring.
- To compare effect of triple procedures on circadian profile and BP using active devices “ABP-051” compared to sham devices.
- To assess therapy efficacy and compliance using stimulator “ABP-051”.
- To assess an immediate stimulation effect from device “ABP-051” on hemodynamic parameters when it is first used in an acute experiment using the continuous BP recording monitor.

It was a randomized, blind, sham-controlled study as it provided randomization of patients to get true and sham stimulation.

Endpoints were:

- BP dynamics during the first stimulation;
- Dynamics of 24-hour BP profile in 2 weeks after the start and 2 weeks after the completion of two-week stimulation course;
- adverse effects of stimulation.

c) Ethical aspects

The study was carried out in accordance with “MEDDEV 2.7/1 Rev 4. Guidelines on medical devices. Clinical assessment: guidelines for manufacturers and authorized bodies”, and Worldwide Medical Association of Helsinki “Ethical principles of scientific and medical research involving humans” dated 1964 with the updates dated in, “Rules of Clinical Practice in the Russian Federation” approved by Order of the Ministry of Health of the Russian Federation” approved by the Order of the

Ministry of Health of the Russian Federation № 266 dated 19.06.2003, National standard of the Russian Federation "Good Clinical Practice" (2005)

d) Patients

1) Inclusion criteria:

- I-III grade essential hypertension;
- BP profile abnormalities;
- stable therapy or its absence during primary diagnostics;
- signed informed consent using the form agreed with the Ethics Committee at FSBI "Almazov National Medical Research Center".

2) Exclusion criteria:

- unwillingness to continue the study;
- presence of unstable conditions;
- change of therapy for less than 10 days prior primary examination;
- presence of conditions corresponding to contraindications enlisted in section 1.1.

3) Population of patients (it is presented on figure 3)

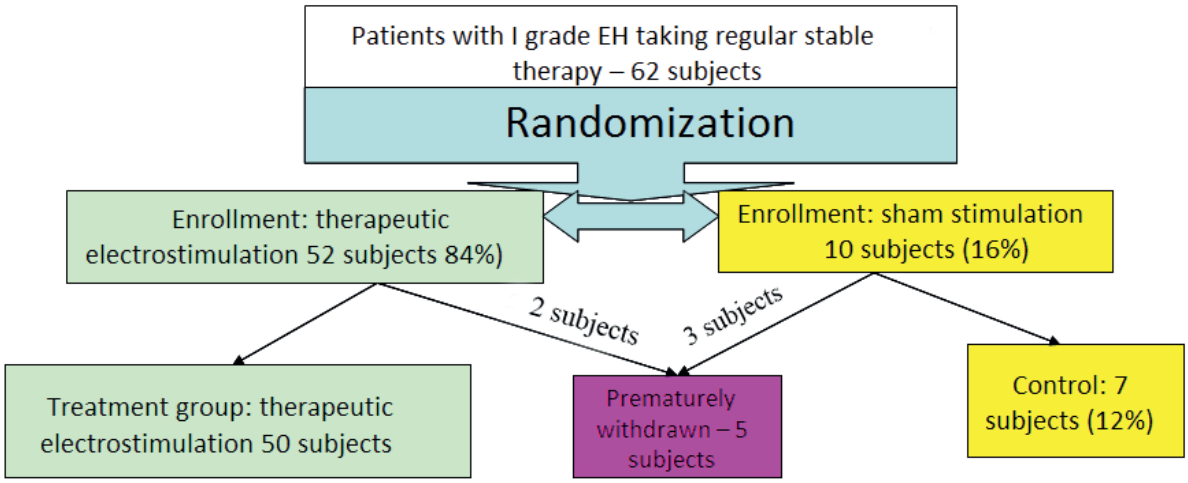


Figure 3 Groups of patients enrolled to the study.

62 patients with I-III grade essential hypertension: patients with II-III grade EH having regular stable therapy and untreated patients with I grade EH randomized to 2 groups were enrolled to the study:

- treatment group of 52 subjects being stimulated by device "ABP – 051";
- 10 subjects having sham stimulation with the active model simulator.

Hemodynamic characteristics of patients in the treatment group based on three-day BP monitoring are presented in table 1. The table shows that approximately 1/2 of patients had increased

BP, while TI index was recorded in 2/3 of patients. Over 1/2 of patients had the increased BP variability, and the decrease of circadian index (insufficient BP decrease during the night) was observed in over 1/3 of patients.

Value	Number of subjects with increased value
Total	50 (100%)
SBP increase during the day	25 (50%)
DBP increase during the day	16 (32%)
TI SBP increase during the day	34 (68%)
TI DBP increase during the day	20 (40%)
VAR SBP increase during the day	28 (56%)
VAR DBP increase during the day	13 (26%)
SBP increase during the night	24 (19%)
DBP increase during the night	19 (38%)
TI SBP increase during the night	33 (66%)
TI DBP increase during the night	22 (44%)
VAR SBP increase during the night	16 (32%)
VAR DBP increase during the night	13 (26%)
CI SBP	17 (34%)
CI DBP	10 (20%)

Table 1 Hemodynamic parameters based on three-day BP monitoring in patients of the treatment group.

At the enrollment, I grade EH was diagnosed in 10 subjects (20%), grade II – in 27 (54%), and grade III EH – in 13 subjects (26%).

Mean SBP and DBP value in office measurement in the treatment group was 137±17 and 82±13 mm Hg, and in sham group: 132±11 and 82±12 mm Hg. And the groups differed significantly by blood pressure level.

e) Examination methods:

1. investigation of acute reaction on stimulation with device “ABP – 051” during continuous BP monitoring using monitor Finometer - pro (FMS, Holland) for the first time. Recording was made for 5 minutes prior, 5 minutes during and 5 minutes after device stimulation in supine position;
2. three-day BP monitoring with measurement frequency every 30 minutes during the day and night (24-hour monitoring devices AD INKRT and BPLab, Russia);
3. assessment of BP level and circadian profile based on reconstruction of three-day monitoring data (fig. 4) using the method of non-sinusoidal variability [G.S. Katinas, M.V. Dementyev, F.

Halberg, et.al. Evaluating the form of nonsinusoidal variations // World Health Journal. 2011. 3(2). P. 135—149.];

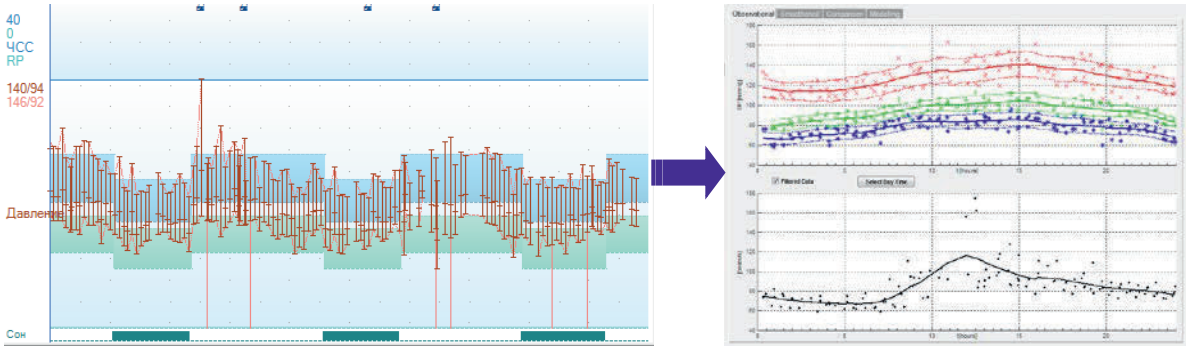


Figure 4 Reconstruction process of three-day monitoring data into BP circadian profile.

e) Study design

The study design is presented on figure 5.

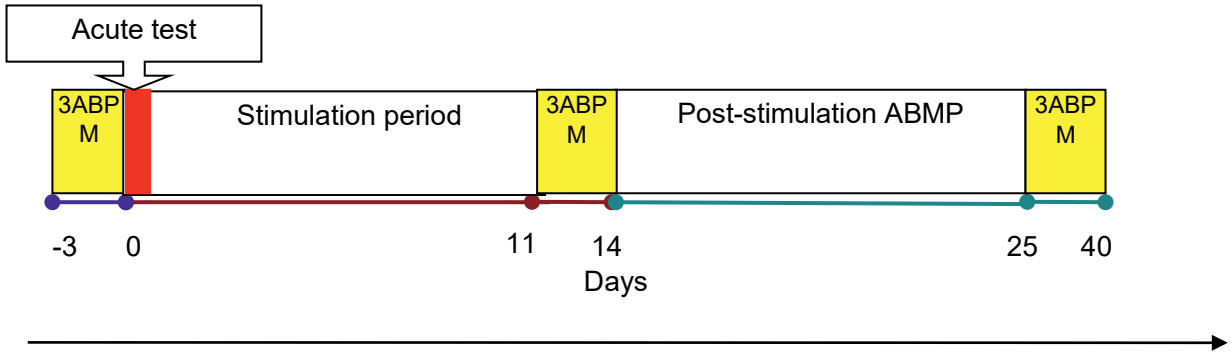


Figure 5 Study design. 3ABPM – three-day BP monitoring.

After initial BP monitoring, if 24-hour BP abnormalities were found, a patient was enrolled to the study. On the same day, acute test was made: investigation of BP dynamics in response to the first stimulation session using continuous recording method. Then in outpatient settings, stimulation using device “ABP – 051” was made during 2 weeks by the recommended methods thrice a day.

On day 12-14, three-day 24-hour monitoring was repeated with reconstruction of BP circadian profile.

On day 26-28, BP circadian profile was finally assessed.

f) Study randomization

Active devices “ABP-051” and their sham devices were visually identical. In the beginning of the study, all devices were numbered randomly by a person not participating in the study. Serial number and assigned local number were kept in the place not available for investigators, and devices were dispensed randomly.

Codes were unblinded after the study completion and stage 1of statistical processing when therapy effect was assessed in each patient. The aim of the second stage was to assess efficacy of active and sham devices.

g) Statistical processing.

Zero hypothesis: effect of course ABP - 051 exposure to BP level and BP circadian abnormalities is not present.

The sample size was calculated with regards to alpha-error 5% to reject the zero with statistical power 80%. Such sample of patients is often used in medical studies: with compliance of the evidence-based medicine principles (good clinical practice – GCP, good laboratory practice – GLP and good statistical medicine – GSP), type of selected patients allows to extrapolate successfully the results to the entire population and confirms the absence of statistically significant differences related to age, sex, disease stage and clinical symptoms.

The database was formed, it included source (crude) results obtained during the three-day BP monitoring, as well circadian profile values obtained during the profile reconstruction. The methods of comparative analysis for unrelated and related population were used for every patient individually and sample in general, comparative analysis was performed. As well, the result of remote exposure and stimulation effect on circadian BP profile delayed for two weeks was compared. Both absolute BP dynamics in the sample and circadian profile changes in each certain case, as well such profile changes as time index, BP variability (VBP) and level of nocturnal BP decrease were considered. The comparative analysis of efficacy of active devices “ABP – 051” and sham devices was performed. Differences at < 0.05 were considered significant. The material was processed using program ”Statistica 10”.

2. RESULTS

a) start date of the clinical study - 27.02.2019**;**

b) completion date of the clinical study - 15.07.2019;

c) location of study subjects:

61 subject live in Saint Petersburg or close neighborhood,

1 – in Novgorod Region, v. Shimsk

d) subject demographic data: all subjects of Caucasian race, age 51±14 year; male/female ratio 42/20.

e) compliance with the clinical examination plan: full compliance with the clinical examination plan, during the examination, the plan was not changed.

Adverse effects in control groups

5 subjects were prematurely withdrawn from the study: 3 due to unwillingness to repeat three-day monitoring or “due to family reasons”, 2 patients due to aggravation of general health condition during the stimulation. And subjects withdrawn from the study were initially enrolled to different groups: two to the treatment group, three to the control group, and patients reporting adverse effects – each one in every group. Thus, the incidence of adverse effects in the groups did not differ, $\chi 2=2.04$; $p=0.15$. Other

patients did not express complaints on health aggravation either during the stimulation or during follow-up after its completion.

Assessment of acute reaction on stimulator using device “ABP – 051”.

Acute reaction to the exposure was assessed during continuous BP recording using non-invasive monitor Finometer-pro (FMS, Holland) with the initial stimulator use. The recording was made during 15 minutes (5 minutes prior, 5 minutes during and 5 minutes after device stimulation) in supine position.

Significant BP decrease was not recorded in any patient during and 5 minutes after the stimulation: 138±14 and 85±18 mm Hg; 137±14 and 85±18, 138±15 and 86±14 mm Hg, respectively. $p>0.05$ was shown for all values.

BP dynamics during course stimulation and in 2 weeks after its completion in control groups

During the course administration, patients being stimulated had a small but dynamics of mean daily BP which was shown by the group during the day as: -1.7±11.1 mm Hg, $p<0.001$ for systolic and -1.2±7.9 mm Hg, $p<0.001$ for diastolic BP. While SBP was increased on 2.7±5.2 mm Hg, $p<0.001$ and DBP on 5.1±10.9 mm Hg, $p<0.001$ in the group of sham stimulation using the sham device.

The analysis of mean daily BP values established that significant BP decrease in the end of stimulation period (on day 12-14) was observed in 23 (46%) patients. 10 (20%) additional patients had a significant BD decrease compared to source data during the third examination – on day 12-14 after the stimulation period (on day 26-28 starting from the study enrollment). Thus, 33 (66%) patients completing the study responded on the process stimulation with significant BP dynamics.

SBP decrease in patients responding to the stimulation during the day was -8.3±7.7 (1.5 – 35.1) mm Hg, $p < 0.001$, while diastolic -5.8±3.8 (1.8 – 16.4) mm Hg, $p<0.001$.

One of the examples of BP change is presented on fig 6.

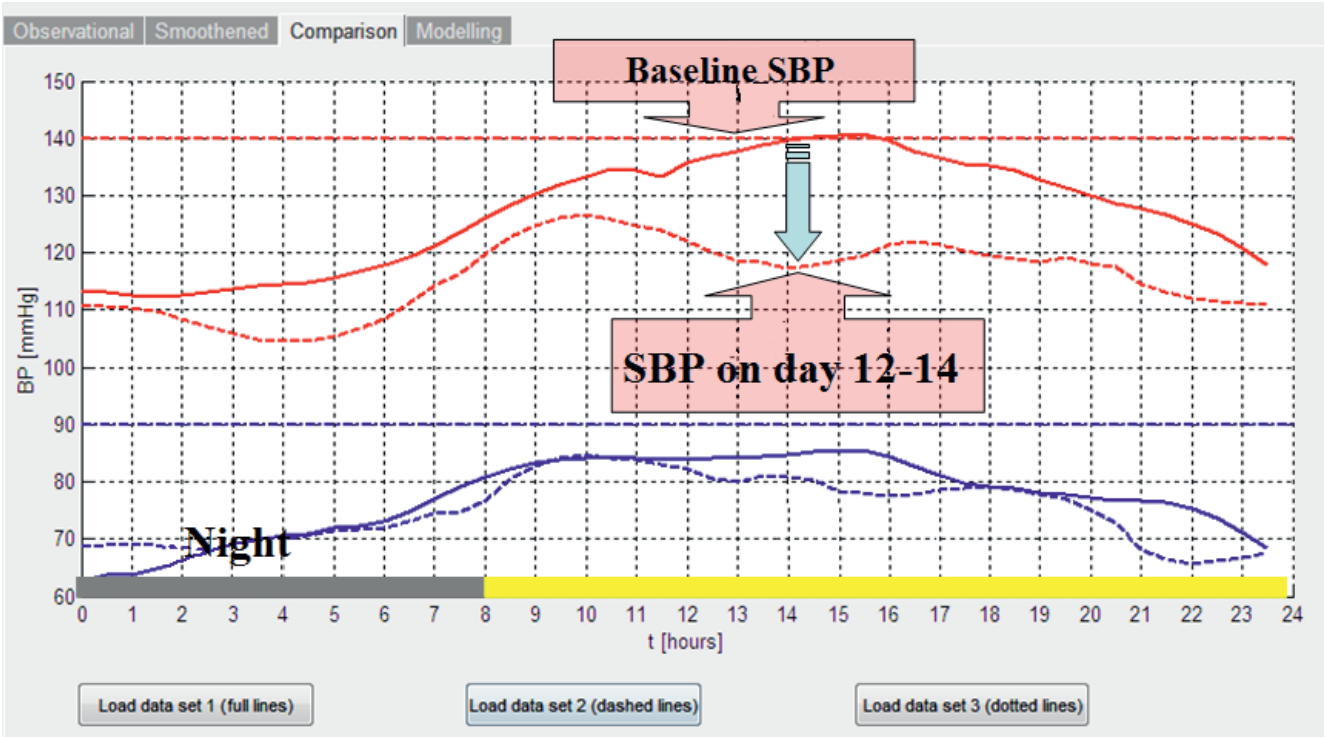


Figure 6 Dynamics of systolic and diastolic BP based on reconstruction of circadian profile in 37-year old patient with I grade EH on day 12-14 days from start of the stimulation.

Assessment of consistency of BP decrease after course administration of device ABP – 051.

To assess consistency of stimulation effect by “ABP-051”, the third examination was made on day 12-14 after the stimulation course (on day 26-28 from the study enrollment). It was established during the study that 10 (20%) patients that did not have dynamics in the end of stimulation period, showed significant SBP and DBP decrease compared to baseline BP value. In general, 20 (40%) patients showed reduced values in relation to baseline BP value. Cumulative dynamics of mean daily blood pressure was illustrated on fig. 7.

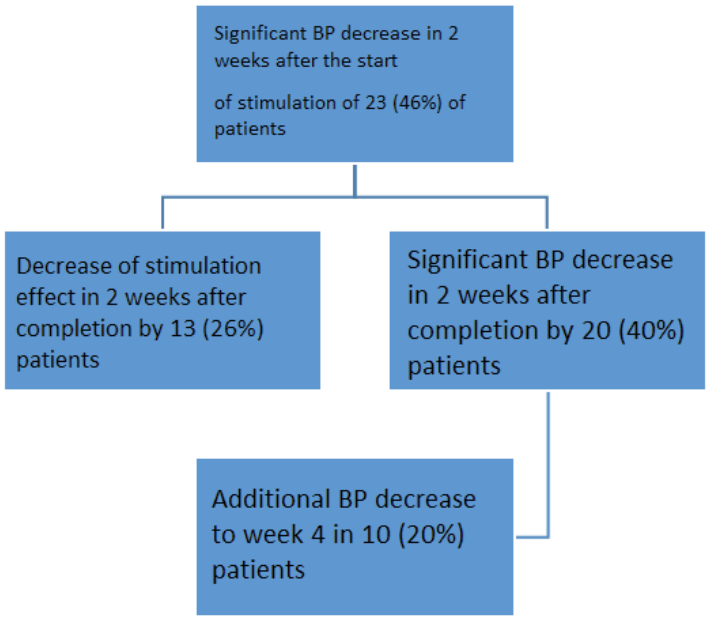


Figure 7 Dynamics of mean daily blood pressure in the end of stimulation period and in 2 weeks after the completion.

One of the patients with BP decreased in 2 weeks after completion of stimulation is presented on figure 8.

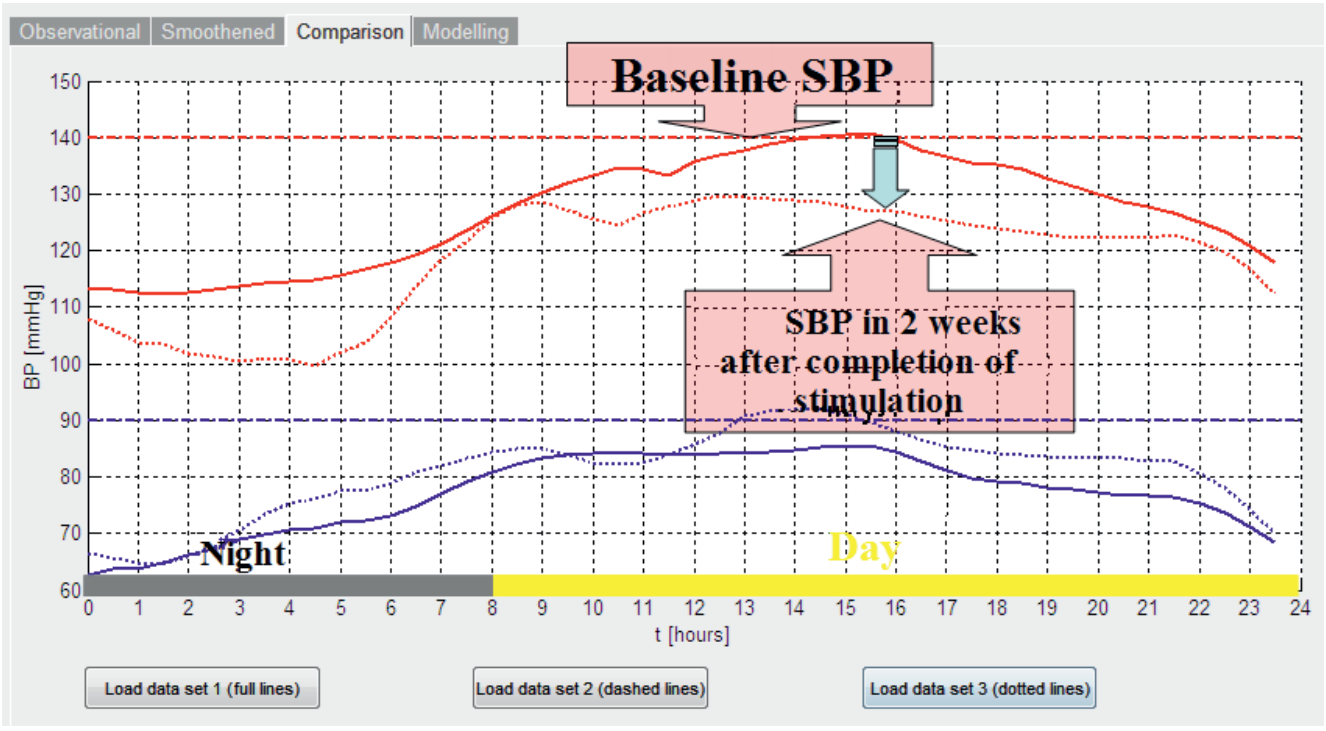


Figure 8 Changes of BP profile on day 26-28 (on day 12-14 after completion of the stimulation) in 37-year old patient with I grade EH.

Along with decrease of mean daily BP during stimulation by “ABP-051”, significant TI decrease both in day and night period. The data is presented on fig. 9.

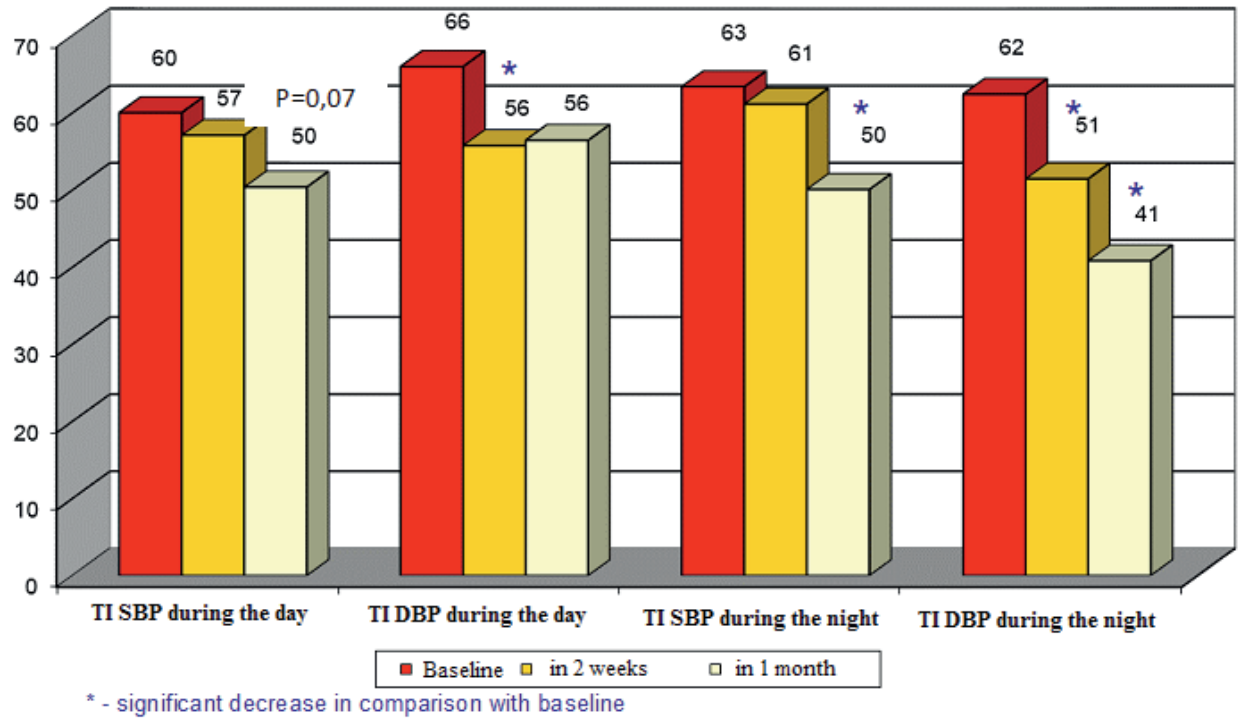


Figure 9 Dynamics of SBP and DBP time index in patients in the end and 2 weeks after completion of stimulation by ”ABP-051”.

It was established that mean value of DBP time index (TI) was significantly decreased in the end of 2-week cycle, while SBP TI was decreased only in 2 weeks after completion.

It was also established that about 1/3 of patients having abnormal value (TI over 20%) normalized the parameter to the end of 2-week course of “ABP-051” administration. The effect maintained at the third monitoring – in 2 weeks after completion of course treatment (the data is presented in table 2).

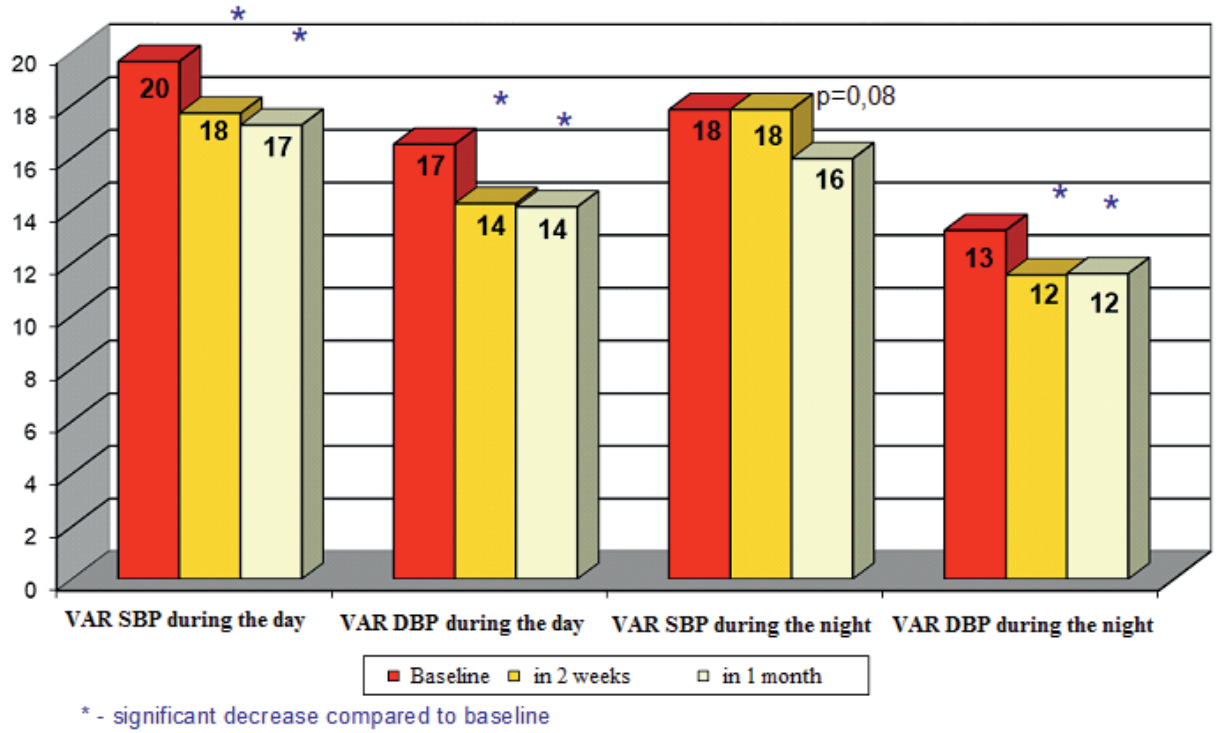
Thus, effect of course “ABP-051” exposure appeared to be at least not inferior to the end of post-stimulation period which also shows its consistency during the month cycle.

	In 2 weeks	In 1 month
TI SPB during the day	18%	15%
TI DBP during the day	15%	15%
TI SBP during the night	24%	18%
TI DBP during the night	23%	23%
TI SBP or DBP during the day или during the night	35%	33%

Table 2 Proportion of patients normalizing time index in the end and in 2 weeks after completion of stimulation cycle by “ABP-051”.

Dynamics of BP circadian values during course stimulation and in 2 weeks after the completion.

Along with values reflecting BP increase, positive dynamics of parameters reflecting its daily profile was observed. The analysis of VAR BP dynamics during course stimulation showed that mean value was decreased both for daily and night VAR DBP values, as well for daily SBP (fig. 10). And in one month after the start of 2 stimulation course by “ABP-051”, decrease of VAR value is not at least decreased (table 3).



Dynamics of SBP and DBP variability in patients in the end and in 2 weeks after completion of “ABP-051” stimulation.

	In 2 weeks	In 1 month
VAR SBP during the day	36%	29%
VAR DBP during the day	46%	23%
VAR SBP during the night	25%	25%
VAR DBP during the night	57%	57%
VAR SBP and/or DBP during the day, and/or during the night	68%	65%

Table 3 Proportion of patients normalizing VAR BP in the end and in 2 weeks after cycle of “ABP-051” stimulation.

Moreover, 2/3 of patients had a normalized value both in the end of stimulation period and in 2 weeks after the completion.

It was also established that 1/3 of patients of the treatment group having the decreased circadian index (CI) at the study onset, during stimulation had its positive dynamics. If circadian index of SBP tended to improve, then CI DBP was increased significantly to the end of the month (fig. 11).

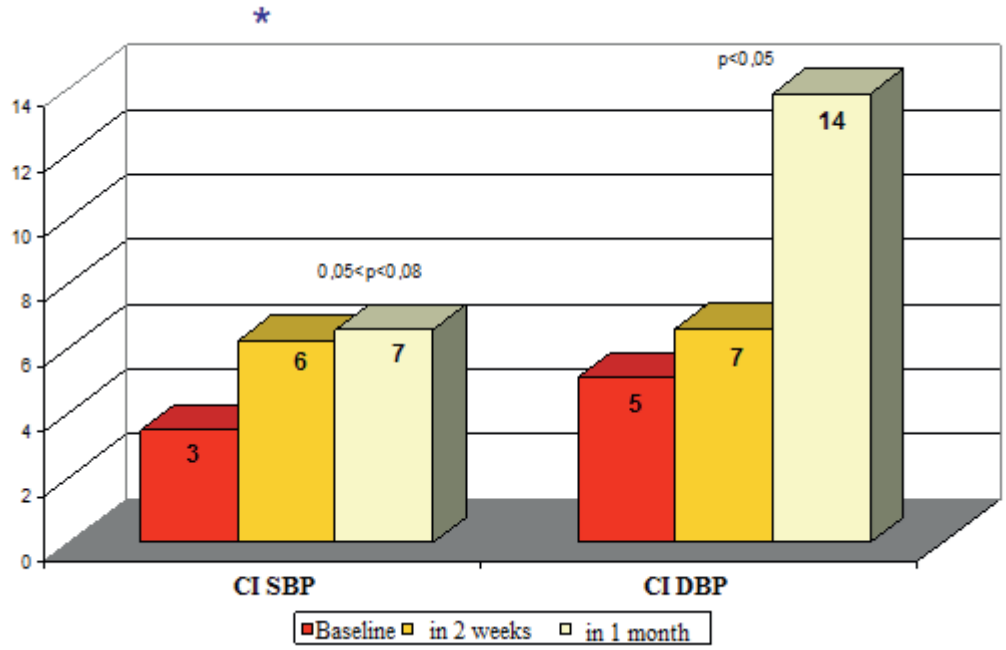


Figure 11 Circadian index in the end and in 2 weeks after completion of stimulation course by “ABP-051”.

Such restoration is demonstrated on fig. 12.

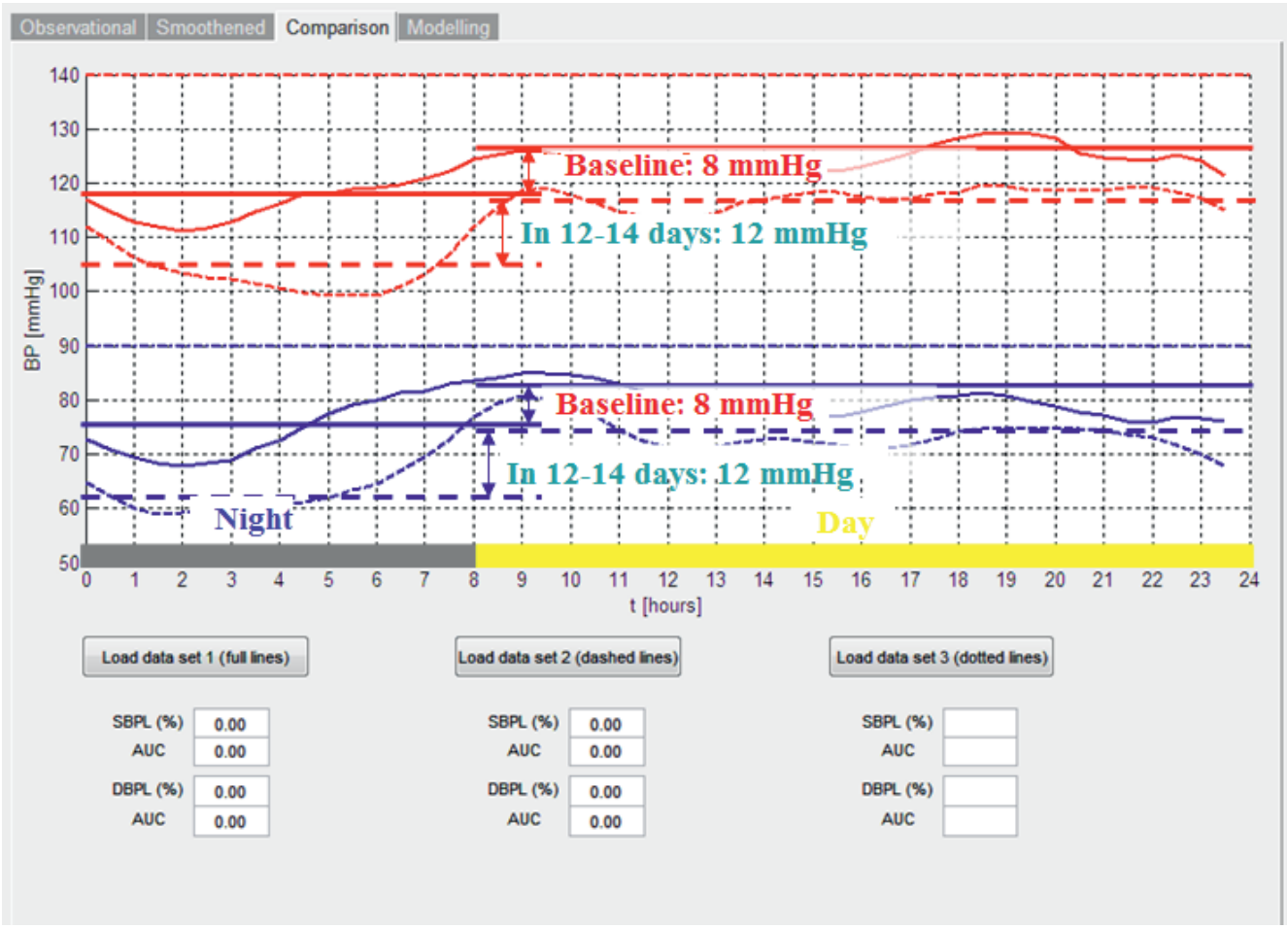


Figure 12 Restoration of circadian index in recurrent monitoring of 69-year old patient S. with III grade EH on day 12-14.

The number of patients normalizing SBP and DBP values was significant both during recurrent (in 2 weeks) and delayed monitoring (in one month). The data is presented on figure 13.

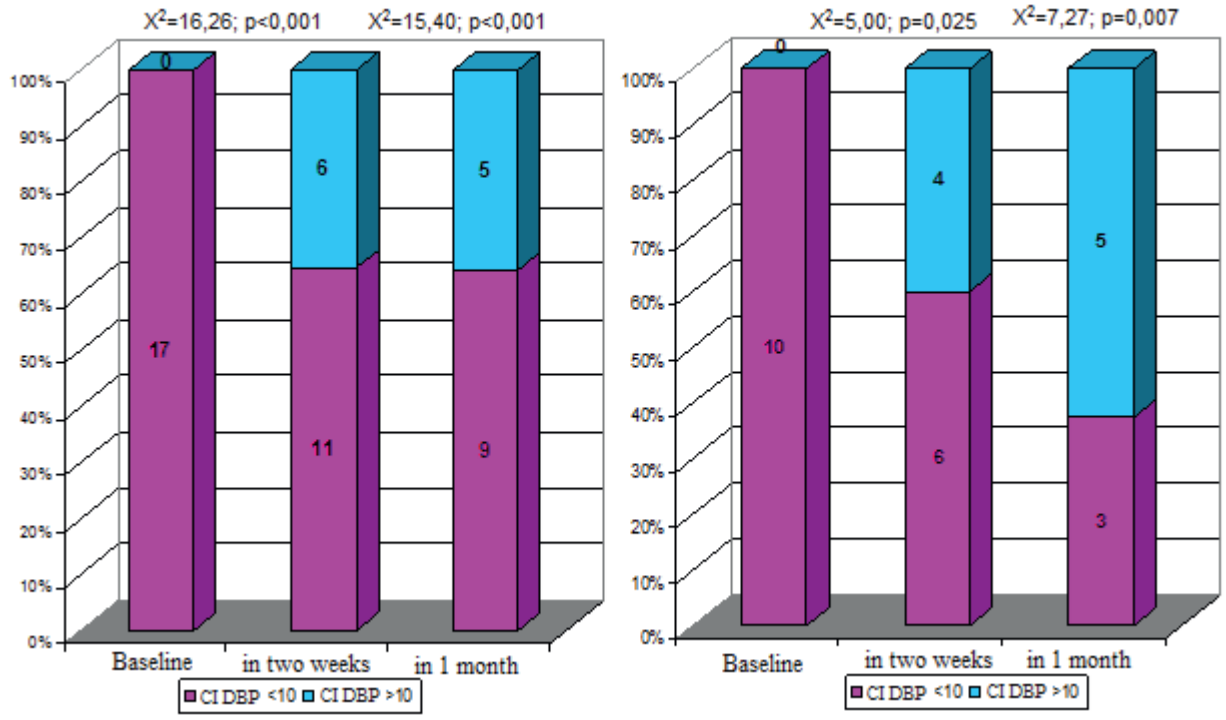


Figure 13 Recovery of circadian index in the end ABP-051 stimulation and 2 weeks after the completion.

Thus, during course stimulation by “ABP-051”, significant normalization of the circadian profile maintaining for 2 weeks after completion was observed.

Cumulative response to course exposure to stimulator “ABP-051”

As it was mentioned above, in the end of stimulation cycle and in 2 weeks after completion, 33 (66%) patients had a significant decrease of blood pressure. And some patients did not show such decrease.

Meanwhile, in the group demonstrating significant dynamics of mean daily BP level, the analysis of BP monitoring established that some patients had normalization of values. And normalization of the values is an independent predictor of prognosis improvement. So it was established in the group that 5 (10%) subjects with initially increased TI SBP and/or DBP had normalized values. The normalization of initially increased VAR SBP and/or DBP was shown in 7 (14%) patients, and 4 (8%) demonstrated normalization of initially decreased CI – the data is graphically presented on figure 14. It should be noted that some patients not responding with significant BP decrease had normalization of several parameters reflecting circadian profile disorder.

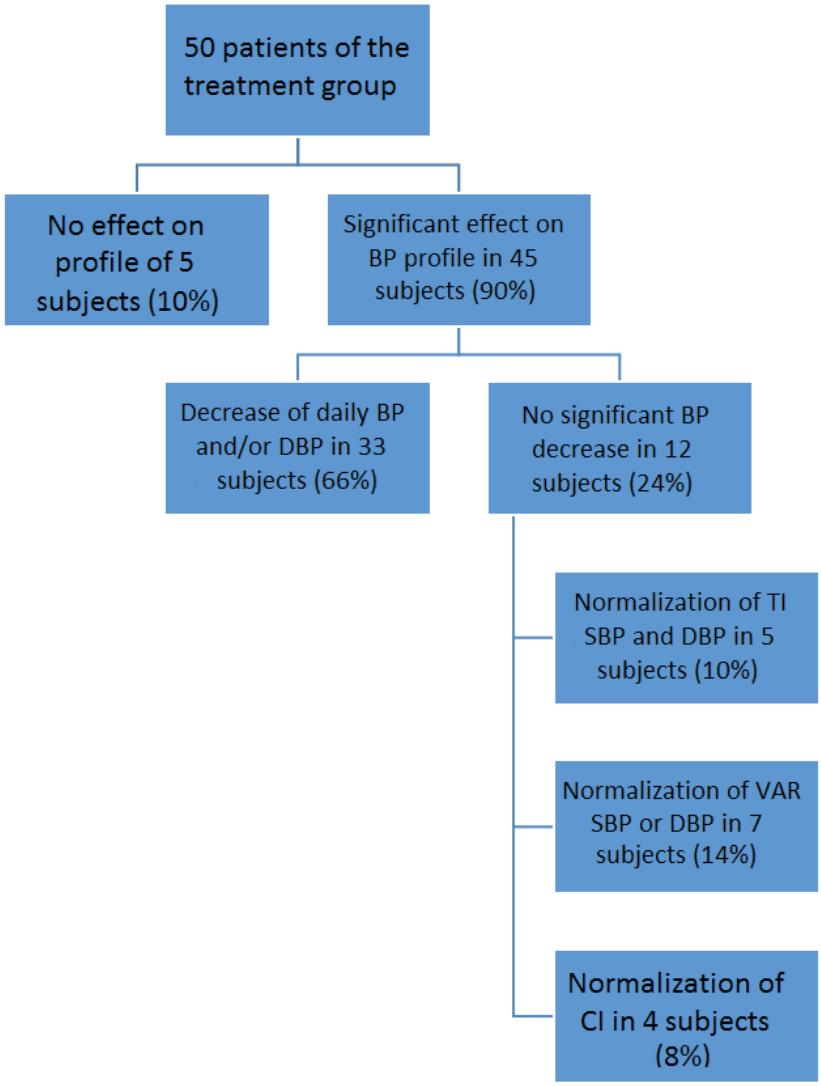


Figure 14 Main effects of course administration of stimulator “ABP-051” (Sum of patients in the lower row is larger than the number of subjects not responding with BP decrease as some of them had normalization of several values).

Thus, the number of non-responders (not responding with any positive effect) on stimulation in the treatment group - 5 subjects (10%). Other patients responded on course stimulation with significant BP decrease and/or normalization of 24-hour BP values. The total number of responders was 45 patients (95%), among them, 12 (24%) patients had recovered values without significant decrease of mean daily BP level.

3. CONCLUSIONS.

- Single course administration of stimulator “ABP-051” leads to a significant decrease of both systolic and diastolic BP compared to baseline value, as well in patients from the sham stimulation group.
- Significant decrease of mean daily BP in response to stimulation by device “ABP-051” was observed in 66% of patients with I-III grade essential hypertension.
- Anti-hypertensive effect was preserved in 40% of patients to the end of the second week after the completion.
- Along with BP decrease in patients as a result of stimulation by device “ABP-051”, normalization of time index, BP variability and circadian index was observed.
- Total proportion of patients responding to course administration of stimulator “ABP-051” with significant BP decrease or normalization of one or another value of 24-hour BP profile is 90%.
- To predict efficacy of “ABP-051”, it is appropriate to use the method of ambulatory BP monitoring as three-day recording with subsequent reconstruction of circadian profile.
- Stimulator “ABP-051” does not induce significant BP fluctuations when used for the first time and is well-tolerated in general being administered as a course.
- Administration of electrostimulator “ABP-051” is not accompanied with more frequent health aggravation compared to the sham stimulation group.
- Longer study is necessary to elucidate a cumulative stimulation effect, as well to clarify reasons and pathways to overcome resistance to ABP-051 therapy.

Study limitations.

The study has provided efficacy assessment of stimulator “AP-051” in one course which does not give any grounds to conclude on efficacy of its regular use in consecutive therapy courses. This disadvantage can be eliminated during investigation of effects of a longer course of the device administration.

4.ABBREVIATIONS AND DEFINITIONS

AH – arterial hypertension~;	BP – blood pressure
EH – essential hypertension	DBP – diastolic blood pressure
SBP – systolic blood pressure	TI – time index
VAR – variability	CI – circadian index

5.ETHICAL ASPECTS

Prior the study, the approval of the ethics committee at FSBI “Almazov National Medical Research Center” approving the patient’s informed consent form, was obtained.

6. EXECUTIVE STRUCTURE.

6.1 BRIEF DESCRIPTION OF THE CLINICAL STUDY ORGANIZATION

The study was carried out in outpatient conditions on the base of the research laboratory of circulation physiology at FSBI “Almazov National Medical Research Center” with compliance of the agreed and approved design project which contents is presented above.

Federal State Budgetary Institution “Almazov National Medical Research Center” of the Ministry of Health of the Russian Federation. Abbreviated name: FSBI “Almazov National Medical Research Center” of MoH of the Russian Federation.

Location of the buildings:

- Main clinical complex and specialized perinatal center are located by address: 197341, Saint Petersburg, Akkuratov Str., 2 (how to get).
- Treatment-rehabilitation complex is located by address: 194156, Saint-Petersburg., Parkhomenko lane, 15 (how to get).
- “Polenov Russian Research Neurosurgical Institute“ (branch of the Federal State Budgetary Institution “Almazov National Medical Research Center” of the Ministry of Health of the Russian Federation) is located by address: 191014, Saint Petersburg, Mayakovsky Str., 12 (how to get).
- Pediatric treatment-rehabilitation complex is located by address: Saint Petersburg, Kolomyazhsky lane, 21, bld. 2

Structure of FSBI “Almazov National Medical Research Center” of the Ministry of Health of the Russian Federation

FSBI “Almazov National Medical Research Center” of the Ministry of Health of the Russian Federation – medical institution of a wide profile in which the following operate:

• outpatient treatment complex (350 beds);
• treatment-rehabilitation center (360 beds);
• perinatal center (130 beds).

Main fields of activity

FSBI “Almazov National Medical Research Center” is a large federal specialized medical institution which profile involves such areas of medicine as cardiology, cardiovascular surgery, transfusiology and cell therapy, rheumatology and endocrinology. The center activity lies not only in rendering highly qualified medical care to population but also training of highly qualified staff to work in the medical area, development of new methods and technologies of treatment of cardiological diseases, research studies.

Types of high technology medical care of the Almazov center:

Abdominal surgery, obstetrics and gynecology, IVF, hematology, neurosurgery, neonatology, oncohematology, oncology, rheumatology, cardiovascular surgery, thoracic surgery, pediatric surgery in a neonatal period, traumatology and orthopedics, heart, bone marrow and “heart-lung” complex transplantation, endocrinology, ophtalmology, urology, maxillofacial surgery, pediatrics.

Medical care in 24-hour inpatient settings:

cardiology, rheumatology, neurology, hematology, pediatrics, obstetrics and gynecology, neonatal pathology, surgery, traumatology and orthopedics, therapy, endocrinology, physiotherapy, reflexotherapy, physiotherapy.

6.2 STUDY PARTICIPANTS:

- Mamontov O.V – research associate of the cardiopulmonology testing laboratory of the research laboratory of circulation physiology of the Heart and Vascular Institute at the Almazov National Medical Research Center,
- Yudina Yu.S. – junior research associate of the research center of essential hypertension and pathogenesis, research unit for essential hypertension,
- Spivak N.A. – laboratory assistant of the research laboratory for electrocardiography,
- Ignatova T. Ch. – research laboratory assistant of the research laboratory for electrocardiography

Responsible executor – Mamontov O.V.

(CV of Mamontov O.V. and Yudina Yu. S. in corresponding annexes).

6.3 SPONSOR REPRESENTATIVES.

Ozhgikhin Ivan Vladimirovich, deputy General Director in development of sales, marketing systems and service support of civil products by “Schwabe” Holding.
Samokhin Andrey Nikolaevich, deputy Director in economy and finances - chief accountant

Signature sheet

I agree with the report contents.

	Full name, position	Date/signature
Sponsor's representatives	I.V. Ozhgikhin Deputy General Director in development of sales, marketing systems and service support of civil products by "Schwabe" Holding A.N. Samokhin deputy Director in economy and finances - chief accountant of "Schwabe –Moscow" LLC	
Study supervisor	A.O. Konradi Deputy in scientific work of FSBI "Almazov National Medical Research Center"	
Study group	O.V. Mamontov Research associate of the cardiopulmonology testing laboratory of the research laboratory of circulation physiology of the Heart and Vascular Institute at the Almazov National Medical Research Center	
	Yudina Yu.S. Junior research associate of the research center of essential hypertension and pathogenesis, research unit for essential hypertension	
	N.A. Spivak Laboratory assistant of the research laboratory for electrocardiography	
	T. Ch. Ignatova Research laboratory assistant	

Annexes. Qualification of the executors:

1. CV of Mamontov O.V.
2. CV of Yudina Yu.S.