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Efficacy and safety of fimasartan, a new angiotensin-receptor blocker, compared to losartan in mild-to-moderate hypertension

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Abstract

Background. A phase III multicenter open-label randomized comparative trial on antihypertensive efficacy and safety of fimasartan and losartan in parallel groups for adult outpatients with arterial hypertension (AH) 1–2 grade during 12 weeks of therapy was performed in 13 investigational sites of Russia. **Design and methods.** The study included patients with mean systolic blood pressure (SBP) in the sitting position ≥ 140 mm Hg and ≤ 179 mm Hg, previously treated patients underwent a «wash-out» period. The starting therapy was fimasartan 60 mg per day or losartan 50 mg per day, in case blood pressure was maintained at the level SBP ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg at 4 and 8 weeks of therapy the doses were increased up to 100 and 120 mg, respectively. Primary end-point was change from baseline in "office" sitting SBP at week 12 that was intended to

show a “non-inferior” fimasartan efficiency (non-significant difference was set at 5.5 mm Hg). **Results.** Altogether 179 patients were randomized either to fimasartan (n = 89) or losartan (n = 90) groups. There were no differences between groups by demographic data and the characteristics of hypertension. After 12 weeks of treatment, mean SBP was 127.7 ± 8,0 mm Hg (–25.2 ± 8.6 mm Hg compared with baseline) in group fimasartan and 127.6 ± 5.6 mm Hg (–24.3 ± 7.8 mm Hg compared with baseline) in losartan group. The mean change in SBP was –0.18 ± 1.00 mm Hg (p = 0.390), the upper limit of the 95 % confidence interval was equal to 1,47 mm Hg that confirms the primary criterion of effectiveness. “Non-inferior” fimasartan efficiency was confirmed by the secondary criteria — the change in SBP and DBP at follow-up visits and the response rate. Safety profiles of fimasartan and losartan were comparable. **Conclusions.** Fimasartan is well tolerated, safe and provides similar to losartan BP lowering effect in outpatient population.

Key words: arterial hypertension, angiotensin II receptor blockers, comparative efficacy, efficacy and safety, comparative trial

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Сравнение антигипертензивной эффективности и безопасности нового представителя класса антагонистов рецепторов к ангиотензину II — фимасартана и лозартана при артериальной гипертензии 1–2 степени

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Резюме

Цель исследования. В 13 исследовательских центрах проведено многоцентровое открытое рандомизированное сравнительное исследование III фазы антигипертензивной эффективности и безопасности антагонистов рецепторов к ангиотензину II фимасартана и лозартана в параллельных группах у амбулаторных взрослых пациентов с артериальной гипертензией (АГ) 1–2 степени через 12 недель терапии. **Материалы и методы.** В исследование включались пациенты со средним систолическим артериальным давлением (САД) в положении сидя ≥ 140 мм рт. ст. и ≤ 179 мм рт. ст.; ранее получавшие лечение больные должны были пройти период «отмывки». Стартовая доза фимасартана составляла 60 мг, лозартана — 50 мг; при САД ≥ 140 мм рт. ст. и/или диастолическом артериальном давлении (ДАД) ≥ 90 мм рт. ст. через 4 и 8 недель от начала терапии дозы увеличивались до 120 и 100 мг соответственно. Первичным критерием эффективности являлось изменение среднего САД (в положении сидя) через 12 недель терапии по сравнению с исходным уровнем с демонстрацией «не худшей» эффективности фимасартана (величина незначимых различий была задана на уровне 5,5 мм рт. ст.) **Результаты.** В популяцию для оценки эффективности и безопасности вошло 179 рандомизированных пациентов: 89 в группе терапии фимасартаном и 90 — в группе лозартана. Группы не различались по основным параметрам, включая демографические данные и характеристики АГ. Через 12 недель терапии среднее значение САД в группе фимасартана составило 127,7 ± 8,0 мм рт. ст. (–25,2 ± 8,6 мм рт. ст. по сравнению с исходными значениями), в группе лозартана — 127,6 ± 5,6 мм рт. ст. (–24,3 ± 7,8 мм рт. ст. по сравнению с исходными значениями). Различия в средней степени снижения САД между группами составили –0,18 ± 1,00 (p = 0,390), верхняя граница 95 % доверительного интервала была равна 1,47 мм рт. ст., что позволило подтвердить первичный критерий эффективности. Подтверждения «не худшей» эффективности фимасартана были получены и при оценке

вторичных критериев динамики САД и ДАД по визитам исследования и количеству ответивших на лечение больных. Профили безопасности фимасартана и лозартана оказались сопоставимыми. **Выводы.** Фимасартан хорошо переносится, безопасен и обеспечивает сопоставимое с лозартаном снижение уровня артериального давления у амбулаторных пациентов с АГ 1–2 степени.

Ключевые слова: артериальная гипертония, антагонисты рецепторов к ангиотензину II, сравнительная эффективность, эффективность и безопасность, сравнительное исследование

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Introduction

Angiotensin II receptor antagonists (sartans) appeared as an option for arterial hypertension (HTN) treatment only in the mid 1990s. But today, the guidelines of international communities consider them as one of the main classes of antihypertensive drugs, and often recommend them as first-line HTN treatment along with the angiotensin-converting enzyme inhibitors [1–2]. This is obvious, since the role of the renin-angiotensin-aldosterone system in the pathogenesis of cardiovascular diseases is undoubted, and drugs modulating its activity take important position in treatment of cardiac diseases. Good antihypertensive efficacy of sartans, their positive effects on target organs, and prognosis were demonstrated in numerous studies [3–6]. Moreover, sartans have a benefit compared to angiotensin-converting enzyme inhibitors: they are better tolerated [7]. Boryung Pharmaceutical Co. Ltd. (Republic of Korea) developed a new agent from the sartan class — fimasartan (Kanarb). The drug was approved for use in Korea for HTN treatment in 2010, and clinical studies demonstrated that their safety is comparable to other sartans [8–9], and they show a slightly more pronounced reduction in blood pressure (BP) compared to losartan [8] and 24-hour antihypertensive efficacy comparable with valsartan [9]. To evaluate its efficacy and safety in the Russian population, a phase III pre-registration multicenter open-label randomized comparative study of antihypertensive efficacy and safety of Fimasartan (Kanarb), produced by Boryung Pharmaceutical Co. Ltd. (Republic of Korea), tablets 60/120 mg per day, and Cozaar (losartan), produced by Merck Sharp & Dohme B. V. (the Netherlands), tablets 50/100 mg per day, was carried out in parallel groups of adult outpatients with HTN stage 1–2 after 12 weeks of treatment in 13 research centers of Russia. Additionally, the pharmacokinetic parameters were evaluated after a single dose of fimasartan in one of the centers. The results of this analysis were presented earlier [10].

Design and methods

Study population

The study involved patients of both sexes aged 18 to 75 years, who were enrolled at least three months after primary HTN 1–2 degree was diagnosed and met the following criteria at the screening visit: average sitting systolic blood pressure (SBP) ≤ 179 mm Hg for patients who had never received antihypertensive therapy, or 140 ≤ SBP ≤ 179 mm Hg for patients receiving antihypertensive treatment, but only when safety and benefits of its discontinuation were awaited; a negative pregnancy test for women of reproductive age. Patients who required the "washout period" from previous antihypertensive therapy, had to meet additional criteria at the randomization visit: SBP ≥ 140 mmHg and ≤ 179 mmHg and a negative pregnancy test for women of reproductive age. Exclusion criteria were the following: HTN 3 degree; in case of treatment by more than one antihypertensive drug; secondary HTN (renal artery stenosis, primary aldosteronism, etc.); known hypersensitivity or contraindications to the study drugs; severe cardiovascular diseases (including heart valve disease and cardiomyopathy); renal insufficiency (creatinine clearance calculated using the Cockroft–Gault formula less than 60 ml/min/1.73 m^2) and medium and severe liver

failure and/or increased transaminase levels — aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) — at least two-fold higher than the upper limit of reference values); human immunodeficiency virus, hepatitis B and/or C, syphilis in past; uncontrolled diabetes mellitus (Hb_{A1c} > 7 %); severe systemic diseases or cancer; drug abuse, alcoholism or mental illness; genetic diseases such as galactose intolerance, congenital lactase deficiency or glucose and galactose malabsorption syndrome; clinically significant laboratory abnormalities; pregnant and breastfeeding women as well as women who do not use adequate contraception.

Study design

The study was conducted within the registration procedure of Kanarb (fimasartan), produced by Boryung Pharmaceutical Co. Ltd. (Republic of Korea), in the Russian Federation. The study was conducted in accordance with the requirements of the Russian legislation and ethical principles.

According to the methodology, it was a phase III multicenter open-label randomized comparative parallel group study. Cozaar (losartan) was chosen as a comparator. It is one of the most well-studied and widely used agents of the angiotensin II receptor antagonist class in the Russian Federation [11].

The study consisted of three phases (periods): screening (up to 14 days), treatment (12 weeks), and follow-up (4 weeks). Duration of the screening period depended on the previous antihypertensive therapy; patients receiving the treatment passed the "washout period" (7 days without taking any antihypertensive drugs), preceded by a period of dose reduction when necessary (not longer than 7 days).

The screening was followed by a 12-week treatment period when patients received either fimasartan or losartan according to randomization. The initial doses of fimasartan and losartan were 60 and 50 mg, respectively. The drug was taken orally, once daily in the morning, at the same time, except for the days of visits, as the evaluation of the clinical efficacy and safety was performed the next morning after the drug intake (BP was measured at each visit in accordance with the recommended procedure by the certified mechanical tonometer after 5 minutes of rest). BP was measured three times at intervals ≥ 1 minute, an average of three measurements was calculated. On visit days, the drug was taken in the research center after the scheduled procedures. The drug doses could be increased up to 120 and 100 mg, respectively, in the following cases: depending on the results of the evaluation by the telephone contact after 2 weeks of treatment (the patient could be invited to unscheduled visit for the therapy correction when necessary); SBP ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg at the planned visits 4 and 8 weeks after treatment initiation.

The following medications were forbidden to administer throughout the study: any other antihypertensive drugs; medicines that could affect the efficiency evaluation, including the regular use of nonsteroidal anti-inflammatory agents, vasodilators, tricyclic antidepressants, etc. (drugs for the treatment of glaucoma without changing the dose throughout the study and acetylsalicylic acid 50–325 mg/day were allowed); tranquilizers, sedatives, hypnotics, neuroleptics; potassium-containing medications; lithium; steroidal hormones (except topical forms), adrenocorticotropic hormone; ketoconazole; drugs that inhibit OATP1B1-transporter.

After completion of the treatment period, the patients were followed up for further 4 weeks; they received the antihypertensive therapy prescribed by a physician-researcher.

Efficiency evaluation

The primary outcome was the change in average SBP (in sitting position) after 12 weeks of treatment as compared to the baseline, showing "not worse" efficacy of fimasartan compared to losartan as an active control.

The secondary outcome measures included: change in average SBP (in sitting position) after 4 and 8 weeks of treatment as compared to the baseline; change in DBP (in sitting position) after 4, 8 and 12 weeks of treatment as compared to the baseline; the number of patients who responded to treatment after 12 weeks of treatment (a response to treatment was defined as the average sitting SBP < 140 mmHg or as the average decrease in SBP > 10 % of the baseline).

Safety evaluation

Safety parameters included: results of clinical assessment at each visit (physical examination

with checkup of systems and organs, measurement of vital signs — BP, heart rate, respiratory rate, and body temperature); ECG data (at screening and randomization visit and after 12 weeks of treatment with the assessment of heart rate and duration of PQ, QT, QTc and QRS intervals); laboratory parameters were determined at each visit, except for the final visit at follow-up, in fasting state, and included clinical and biochemical blood tests (with the assessment of lipid profile at the baseline and at the end of treatment), urinalysis with the calculation of glomerular filtration rate using the modified Cockroft–Gault formula, urine pregnancy test in women of childbearing age); the number of patients (%) who required dose reduction or discontinuation of the study drug due to side effects; adverse events, including serious ones, recorded from the enrolment of the patient in the study until its completion.

Sample size calculation

The calculations were made manually and were reproduced in Stata 12 validated statistical package using SSI module. Based on the published results of phase III clinical study [8], the following baseline data were used for this study: 1) the study should have been conducted as a 'non-inferiority trial', i. e. the effect of the study drug had to differ from the reference one not more than by the value of insignificant differences. The latter was defined as half the difference between the placebo effect which was 7 mmHg for SBP [12] and the magnitude of fimasartan effect which was 18 mmHg [8], so constituting 5.5 mmHg; 2) the standard SBP deviation in patients receiving fimasartan was 13 mmHg [8]. To calculate the sample size in each group, a special formula was used [13] — upon the statistical significance of 5% and achievement of the desired output of 80%, the study had to include at least 140 patients (70 patients per each group). Considering the expected 20% early withdrawal of patients or inapplicable data, we had to include not less than 176 patients for randomization in the ratio of 1:1 (88 per each group).

Statistical analysis

As a full analysis set (FAS) for efficacy, ITT population was used (all randomized patients who had at least one evaluation for the efficacy analysis after treatment initiation) with the confirmation of data in PPS population (probability proportional to size; all patients who completed the study according to the protocol). All randomized patients who took at least one dose of the study drug or the comparator, were eligible for the safety evaluation.

The data are presented as mean ± standard deviation, the differences were considered significant at the 5% level of significance.

Hypothesis for the primary outcome measure was tested using mixed linear models which take into account the center effect as random, and the treatment group effect as fixed. Baseline SBP in the study arm was included in the model as a covariate (fixed effect). To test parameter changes within the group, the paired Student's t-test or Wilcoxon sign test was used. Comparison of changes between treatment groups for baseline SBP and DBP levels and SBP and DBP levels at the study visits was carried out using a mixed linear model which included the research center as a random effect. Baseline SBP and DBP and the treatment group were included in the model as covariates (fixed effect). The treatment groups were compared using the Mantel–Haenszel test with control by the research center.

To evaluate safety, physical examination results were described as discrete variables; results of electrocardiograms and laboratory tests were described as discrete and continuous data by study visits; changes in relation to the baseline for each visit were also analyzed. Comparison of treatment groups was performed using the Fisher's exact test (for deviations from the reference values) and the Student's t-test (or Wilcoxon sign test). The mean values in the treatment groups at visits were compared using the unpaired Student's t-test or nonparametric Mann–Whitney test.

The change in the dose of drugs was described by study visits, as well as for the time of the treatment period, followed by a comparison of treatment groups by types of dose correction. Comparison of groups in discrete variables was performed using the chi-square test or Fisher's exact test.

Study-related adverse events (Treatment Emergency Sign and Symptoms, TESS) were considered adverse events which began at the moment of the first dose intake or later. All adverse events were coded in accordance with

the Medical Dictionary for Regulatory Activities (MedDRA) (version 16.1). Adverse events of the study (TESS) were described with absolute and relative frequencies (the number of patients with adverse events and the number of these adverse events in the group), grouped by system-organ classes (SOC) and preferred medical terms (PT). Treatment-emergent adverse events (TESS) were also divided by severity and relation to the intake of the study drugs. Comparison of the treatment groups by the number of patients with TESS was performed using the Fisher's exact test (for unordered categories).

Results

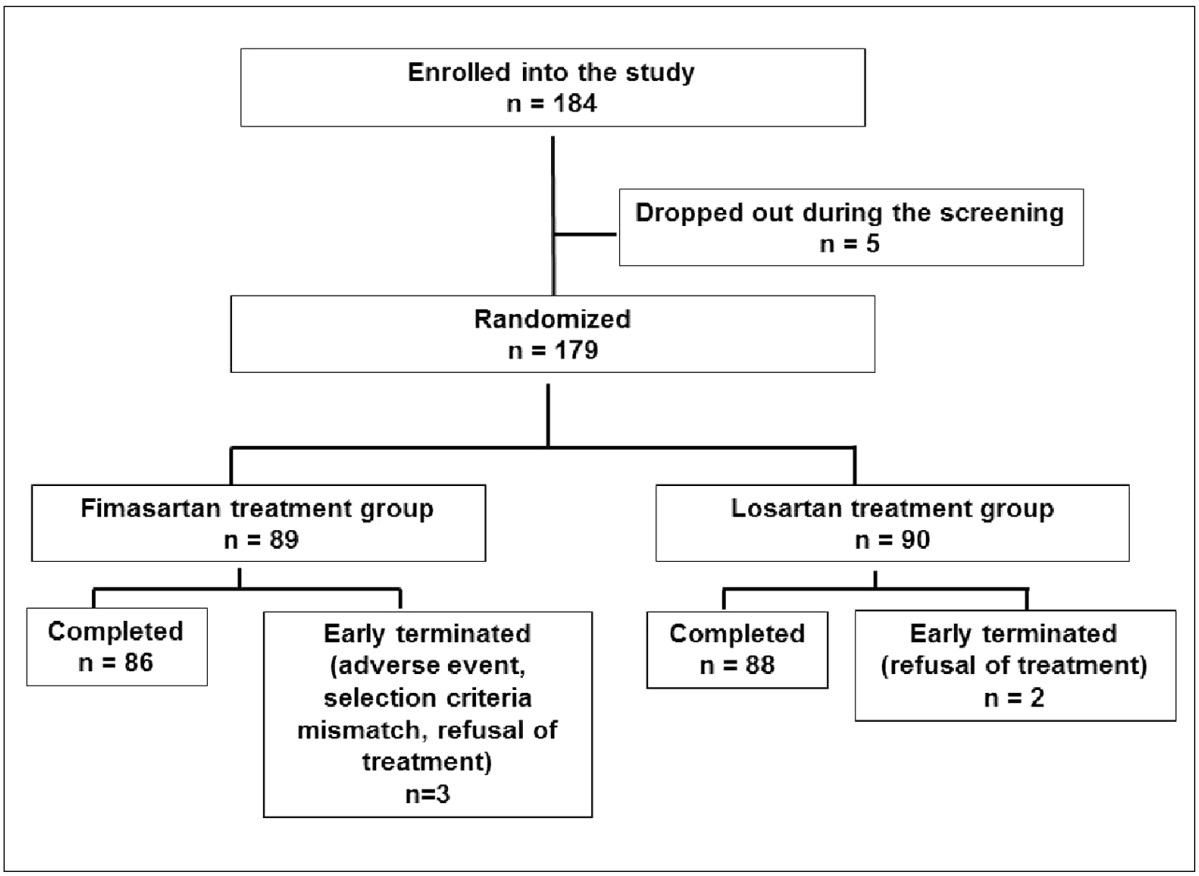
General characteristics and distribution of patients

Total 184 patients were enrolled in the study, 5 patients dropped out during the screening period due to the mismatch with the study selection criteria. 179 patients were randomized: 89 patients in the fimasartan treatment group and 90 in the losartan treatment group (Fig. 1).

Most patients completed the study according to the protocol: 86/89 (96.6%) patients in the fimasartan treatment group and 88/90 (97.8%) patients in the losartan treatment group. In the fimasartan treatment group, 3/89 (3.4%) patients terminated the study earlier: one of them terminated the study due to an adverse event (clinically significant increases in ALT and AST), the second one — due to the mismatch with the inclusion/exclusion criteria, and the third one discontinued participation in the study voluntarily. In the losartan treatment group, 2/90 (2.2%) patients terminated the study earlier voluntarily. Thus, ITT population was 179 patients, and FAS population and the safety analysis population coincided with ITT population. PPS population included 163 patients: 81 patients in the fimasartan treatment group and 82 patients in the losartan treatment group.

The treatment groups did not differ either in demographic or anthropometric parameters, BP level, HTN severity and duration, the number of patients who have previously received antihypertensive therapy and classes of antihypertensive

Figure 1. Distribution of patients during the study



Table

OCHARACTERISTICS OF PATIENTS FROM THE STUDIED GROUPS (n = 179)

Parameter	Fimasartan group. n = 89	Losartan group. n = 90	p
Age. yr	53.4 ± 12.2	53.8 ± 10.0	0.956
Gender, n (%)			0.641
Male	59 (66.3%)	56 (62.2%)	
Female	30 (33.7%)	34 (37.8%)	
Race, n (%)			0.246
European	87 (97.8%)	90 (100.0%)	
Other	2 (2.2%)	0 (0.0%)	
Height, cm	168.4 ± 9.9	170.0 ± 9.2	
Weight, kg	83.4 ± 16.3	83.4 ± 12.6	
BMI, kg/m^2	29.4 ± 5.1	28.9 ± 3.8	0.700
HTN duration, yr	5.8 ± 5.2	6.2 ± 6.6	0.844
Hypertension degree, n (%)			0.309
1	20 (22.5%)	27 (30.0%)	
2	69 (77.5%)	63 (70.0%)	
Smoking, n (%)			0.969
Never	63 (70.8%)	62 (68.9%)	
Current	19 (21.3%)	21 (23.3%)	
Former	7 (7.9%)	7 (7.8%)	
Current smoking			0.879
Duration, years	31.3 ± 10.6	26.8 ± 10.8	0.196
The mean number of cigarettes smoked per day	11.7 ± 7.2	12.0 ± 6.6	0.879
Former smoking			
Duration, years	18.4 ± 3.5	20.0 ± 7.2	0.943
The mean number of cigarettes smoked per day	12.9 ± 7.0	15.7 ± 5.3	0.400
Alcohol consumption, n (%)			0.702
Never	25 (28.1%)	23 (25.6%)	
Former	12 (13.5%)	9 (10.0%)	
Current, occasionally	52 (58.4%)	57 (63.3%)	
Unknown	0 (0.0%)	1 (1.1%)	
Units of alcohol / day	1.0 (0.7)	1.0 (0.9)	0.450
Past antihypertensive medication, n (%)			0.176
No	34 (38.2%)	44 (48.9%)	
Yes	55 (61.8%)	46 (51.1%)	
Imidazoline receptor agonists	0 (0.0%)	2 (2.2%)	
Beta-blockers	6 (6.7%)	5 (5.6%)	
Calcium antagonists (dihydropyridines)	6 (6.7%)	3 (3.3%)	
Diuretics	12 (13.5%)	11 (12.2%)	
ARB	12 (13.5%)	9 (10.0%)	
ACE inhibitors / Diuretics	1 (1.1%)	0 (0.0%)	
ACE inhibitors	33 (37.1%)	30 (33.3%)	

Note: BMI — body mass index; HTN — arterial hypertension; ARB — angiotensin II receptor blockers; iACE — angiotensin-converting enzyme inhibitors. The data are presented as mean and standard deviation.

medications, co-morbidities and risk factors, previous and concomitant treatment. The characteristics of the patients are shown in the Table.

In the majority of patients, HTN 2 degree was diagnosed: in 69/89 (77.5%) patients in the fimasartan treatment group and 63/90 (70.0%) subjects in the losartan treatment group. More than half the patients in both groups previously had received antihypertensive therapy, which in about 40% included the drugs that affected the renin-angiotensin-aldosterone system. On average, 80% of patients in both groups had co-morbidities, often related to metabolism and nutrition disturbance: in 46/89 (51.7%) patients in the fimasartan treatment group and 42/90 (46.7%) in the losartan treatment group. Lipid-lowering and antithrombotic drugs were the most frequently prescribed concomitant drugs: 6/89 (6.7%) and 9/90 (10%); 11/89 (12.4%) and 15/90 (16.7%) for the fimasartan and losartan treatment groups, respectively.

Efficacy evaluation

Baseline average SBP was 152.9 ± 5.9 and 151.9 ± 5.9 mmHg in the fimasartan and losartan treatment groups, respectively. After 12 weeks of treatment, the average SBP was 127.7 ± 8.0 (–25.2 ± 8.6 mmHg compared with the baseline values) and 127.6 ± 5.6 mmHg (–24.3 ± 7.8 mmHg compared with the baseline values) in the fimasartan and losartan groups, respectively. Intra-group changes were significant ($p < 0.001$), and inter-group changes in average SBP reduction after 12 weeks of treatment did not differ significantly ($p = 0.390$). Differences in the average degree of SBP reduction as compared to the baseline between the fimasartan and losartan groups amounted to –0.18 ± 1.00, the upper limit of 95% confidence interval was equal to 1.47 mmHg. Considering the set value of insignificant differences between the groups (+5.5 mmHg), the primary outcome measure was confirmed, therefore, fimasartan is not inferior to ("not worse than") losartan in reducing the average SBP (in sitting position) after 12 weeks of treatment as compared to the baseline.

Similar results were obtained for the secondary outcome measures. Changes in the average SBP per visit are presented in Figure 2.

After 4 weeks of treatment, the reduction in the average SBP compared with the baseline values was –19.7 ± 10.3 and –17.6 ± 10.5 mmHg in the fimasartan and losartan treatment groups, respectively ($p < 0.001$ for intra-group differences and $p = 0.118$ for inter-group differences). After 8 weeks of treatment, the reduction in the average SBP achieved –23.5 ± 9.0 and –23.9 ± 8.6 mmHg in the fimasartan and losartan treatment groups, respectively. Intra-group changes were significant ($p < 0.001$), but there were no inter-group differences ($p = 0.662$). Changes in the average DBP per visit are presented in Figure 3.

Baseline average DBP in sitting position did not differ between the treatment groups ($p = 0.572$). Interestingly, after 4 weeks of treatment, reduction of the average DBP in the fimasartan group was higher (–9.5 ± 9.1 and –7.4 ± 7.5 mmHg in the fimasartan and losartan treatment groups, respectively; $p = 0.018$). However, after 8 and 12 weeks of treatment, the reduction of the average DBP was similar, and no significant differences between the groups were found (–10.3 ± 9.5 vs. –10.7 ± 7.9 mmHg, p = 0,579; and –10.6 ± 8.8 vs. –11.3 ± 7.8 mmHg; $p = 0.466$ in the fimasartan and losartan treatment groups after 8 and 12 weeks, respectively).

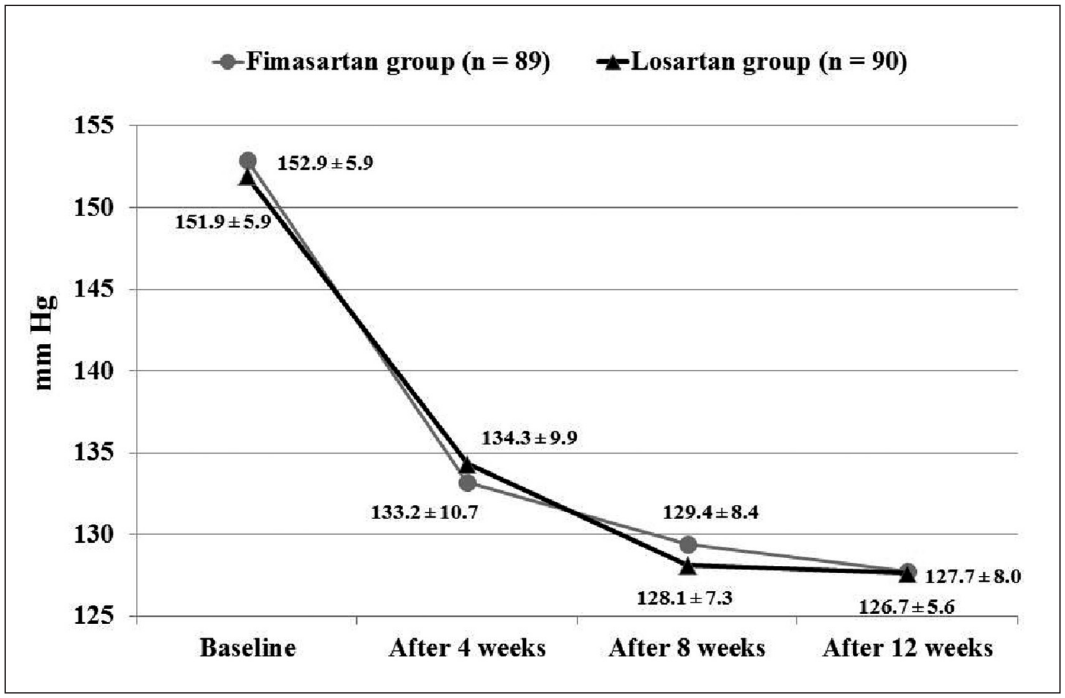
The number of responders to the treatment — reduction in SBP (in sitting position) < 140 mmHg or reduction in SBP > 10% of the baseline after 12 weeks of treatment — were similar in both groups: 85/89 (95.5%) and 90/90 (100.0%) patients in the fimasartan and losartan groups, respectively ($p = 0.143$).

In most patients the dose was unchanged during the study: in 61/89 (68.5%) patients in the fimasartan treatment group and 56/90 (62.2%) patients in the losartan treatment group. The fimasartan and losartan groups did not differ in portions of patients who required increased doses of the drugs: 28/89 (31.5%) against 34/90 (37.8%), respectively; $p = 0.433$, and the average duration of the drug administration with no dose adjustment ($p = 0.121$). Compliance was satisfactory, and the treatment groups did not differ in the number of patients with the compliance between 80 to 100% throughout the study: 83/89 (93.3%) and 83/90 (92.2%) in the fimasartan and losartan treatment groups, respectively ($p = 0.792$).

Safety analysis

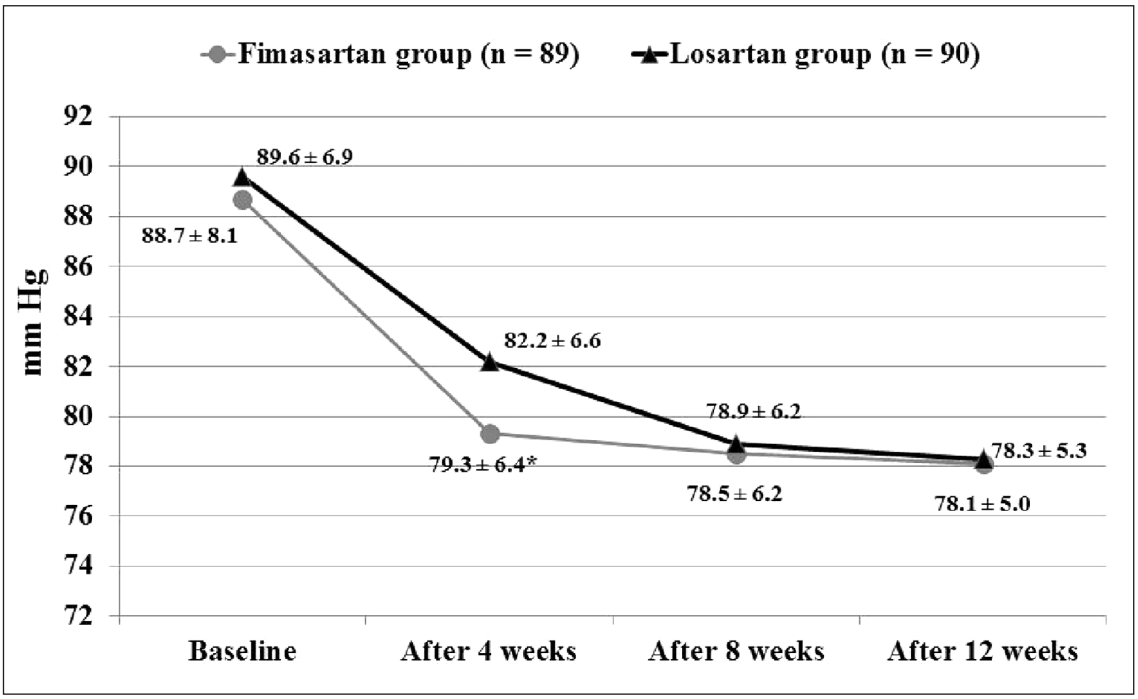
Various adverse events were reported in 20/89 (22.5%) patients of the fimasartan treatment group

Figure 2. Changes of systolic blood pressure



Note: p > 0.05 — for the differences between groups; p < 0.05 — for comparison with baseline at each visit. The data are presented as mean ± standard deviation.

Figure 3. Changes of diastolic blood pressure



Note: * — p < 0.001 significant differences between the groups after 4 weeks of treatment; p > 0.05 — for other visits; p < 0.05 — as compared to baseline at each visit. The data are presented as mean ± standard deviation.

and in 15/90 (16.7%) patients of the losartan treatment group (TESS): 29 and 23 cases in the fimasartan and losartan treatment groups, respectively (p = 0.352). The majority of adverse events were considered as mild and, according to the researchers' assessment, they were not related to the study drugs. Moderate adverse events were observed in 4/89 (4.5%) patients in the fimasartan treatment group, 5 adverse events in total (elevated BP up to 178/110 mmHg, significant increase in AST and ALT, bruised right knee, respiratory infection); moderate adverse events were observed in 1/90 (1.1%) patient in the losartan treatment group, one adverse event in total (irritable bowel syndrome). One adverse event considered as severe (headache) was observed in 1/89 (1.1%) patient in the fimasartan treatment group. The study drug was canceled due to adverse events only in one patient (1.1%) in the fimasartan treatment group (increased ALT and AST levels).

No serious adverse events were reported during the study. Adverse events which occurred during the study were classified into a variety of system-organ classes, but gastrointestinal tract disorders, respiratory infections, headache and nausea were reported most frequently, and their frequency did not differ by treatment groups.

In addition, there was no difference between the fimasartan and losartan treatment groups either in average values or average values of change compared with the baseline data of physical examination, vital signs, and ECG data. Clinically significant abnormalities in blood test parameters were rare, and no differences in the frequency of abnormal results of clinical and biochemical blood tests and urine test parameters were identified between two groups at all study visits.

Discussion

During the study, efficacy and safety of a new nonpeptide angiotensin II receptor antagonist fimasartan were evaluated in the Russian population for the first time. The findings proved that, in terms of efficacy, fimasartan is at least not inferior to losartan (has "no worse" efficacy), both in respect of the primary endpoint — the average SBP reduction after 12 weeks, and in respect of all secondary endpoints for the decrease in the average SBP and DBP per visit (4, 8 and 12 weeks of treatment). The results are substantially similar to the efficacy data for the Korean population [8, 9, 14]; the absence of significant differences in the pharmacokinetic profile of the drug may serve as an explanation in this case [10]. To achieve the target BP level, initial dose of fimasartan of 60 mg was enough in more than 50%, the response rate was almost 100%, and the drug intake led to a persistent antihypertensive effect with a constant increase in efficiency during a three-month follow-up. Persistent antihypertensive effect was observed in the past when assessing both "office" and outpatient indicators (daily BP monitoring): after 8 weeks of treatment, fimasartan was even more effective than valsartan in reducing 24-hour BP level [9]. The data on the differences in the average DBP between fimasartan and losartan treatment groups after 4 weeks of treatment are also worth mentioning. Despite the lack of significance during follow-up, in Korea the study was conducted with a similar patient population, but, as the primary endpoint, the change in average DBP levels after 12 weeks of treatment was assessed [8]. The results showed that fimasartan was more effective than losartan in reducing the average DBP. Perhaps, our study lacked the statistical power to detect this effect, since all calculations were carried out to demonstrate "not worse" fimasartan efficiency as compared to losartan and, first of all, regarding SBP.

Our study showed no significant differences between fimasartan and losartan safety profiles, as well as no new (previously unknown) adverse events/side effects were reported. Both drugs were well tolerated and demonstrated similar frequency, intensity, and nature of the reported adverse events; physical examination data and vital signs, ECG, laboratory parameters at follow-up; the number of patients who required a dose reduction or withdrawal of the study drug due to the side effects. Most reported adverse events were mild in severity. No serious adverse events were recorded. Only for one patient in the fimasartan treatment group, the study drug was withdrawn due to an adverse event — increased levels of liver transaminases, which also corresponded to the previous findings about rare cases of increased AST and ALT levels, during fimasartan treatment (120 mg daily), and their normalization after discontinuation of the drug [8, 9, 14]. This is also true for other drugs of the angiotensin II receptor

antagonist class [15, 16]. Our results on efficiency and safety in the Russian population give additional data to the major observational study conducted in Korea (14,000 hypertensive patients). Our results confirmed the excellent tolerability and efficacy of fimasartan in the real clinical practice that had a favourable effect on the patients' compliance which is one of the most urgent problems in hypertensiology [14].

Conclusions

The results of the study suggest that fimasartan (Kanarb) is well tolerated, safe, and provides BP reduction comparable with losartan (Cozaar) in outpatients with HTN 1–2 degree. These results allow to receive permission for fimasartan use in the Russian Federation, and a new, effective drug of this class will be available to Russian patients. In 2013, the fixed combination of fimasartan and hydrochlorothiazide received approval for use in Korea [17], and such combined fixed forms of the drug with amlodipine (NCT02152306), rosuvastatin (NCT02166814), and the triple combination with amlodipine and rosuvastatin (NCT02569814) are currently in the late stages of research. This suggests that soon most rational combinations of angiotensin II receptor antagonists and other classes of drugs will be available for fimasartan for a wide range of HTN patients.

Conflict of interest

The authors declare no potential conflict of interest.

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