EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 3
316-322
Year: 2020

A COMPARATIVE, RANDOMIZED, DOUBLE BLIND, MULTICENTRIC, ACTIVE CONTROLLED, PARALLEL GROUP, TWO ARM, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF FIMASARTAN TABLETS VS. LOSARTAN TABLETS IN PATIENTS WITH MILD ESSENTIAL HYPERTENSION

[1]*Dr. Shailesh Singh, [2]Dr. Karuna Ramteke, [3]Khushwant Khatri and [4]Pravin Hule

[1]Sr. Vice President, Ajanta Pharma Limited, Advent Research Centre, Plot No. 43 AB and 44 BCD, Govt. Industrial Estate, Charkop, Kandivali (W), Mumbai – 400067.
[2,3]Assistant Manager, Ajanta Pharma Limited, Advent Research Centre, Plot No. 43 AB and 44 BCD, Govt. Industrial Estate, Charkop, Kandivali (W), Mumbai – 400067.
[4]Senior Executive, Ajanta Pharma Limited, Advent Research Centre, Plot No. 43 AB and 44 BCD, Govt. Industrial Estate, Charkop, Kandivali (W), Mumbai – 400067.

***Corresponding Author: Dr. Shailesh Singh**
Sr. Vice President, Ajanta Pharma Limited, Advent Research Centre, Plot No. 43 AB and 44 BCD, Govt. Industrial Estate, Charkop, Kandivali (W), Mumbai - 400067.

Article Received on 01/01/2020 **Article Revised on 22/01/2020** **Article Accepted on 12/02/2020**

ABSTRACT

Background: The present study was designed to evaluate the efficacy, safety and tolerability of Fimasartan Tablets vs. Losartan Tablets in Patients with Mild Essential Hypertension. The main objective of the study was to evaluate mean reduction in the sitting clinic SBP from baseline to Day 90 (±2) after 10 minutes rest period, mean reduction in the sitting clinic DBP from baseline to Day 90 (±2) after 10 minutes rest period, mean reduction in ABPM Parameters from baseline to Day 90 (±2) (Mean 24hour SBP and DBP, Mean Day Time SBP and DBP, Mean Night Time SBP and DBP). **Method:** It was a comparative, randomized, double blind, active controlled, parallel group, two arm, multicentric clinical trial conducted in 13 center across India in patient with Mild Essential Hypertension. The recruitment has been started from Oct 10, 2017 to Feb 03, 2018. Total 215 patients (aged 18-65 years) were randomized in the ratio 1:1 in both arms. All the patients were advised to take one tablet daily either Fimasartan Tablets or Losartan Tablets in the morning as per randomization. The treatment continued for 90 days with periodic follow up on 7^{th}, 15^{th}, 30^{th}, 60^{th} and 90^{th} days from start of treatment. **Result:** The current study showed the mean reduction in systolic blood pressure and diastolic blood pressure as 14.48 mmHg and 9.46 mmHg respectively for Fimasartan tablets and 13.91 mmHg and 8.79 mmHg respectively for Losartan tablets. There were 19 adverse events reported (Fimasartan; 05, Losartan; 13) in the study and which were mild in nature. **Conclusion:** Fimasartan Tablets 60 mg / 120 mg was Non-Inferior to Losartan 50 mg / 100 mg in terms of efficacy and safety in the treatment of patients with mild essential hypertension.

INTRODUCTION

Hypertension is the most common risk factor for vascular disease, including stroke and ischemic heart disease, and the beneficial effects of antihypertensive drugs on reduction of vascular morbidity and mortality have been well established. In clinical trials, antihypertensive therapy has been associated with reduction in stroke incidence, averaging 35% to 40%; myocardial infarction, averaging 20% to 25%; and heart failure, averaging 50%. Among the different classes of antihypertensive drugs, angiotensin receptor blockers (ARBs), which interfere with the renin-angiotensin aldosterone system and restrict the action of angiotensin II, are often prescribed as a first-line therapy because they offer several advantages.[1]

ARBs have a favorable safety profile compared with that of other antihypertensive agents. Their safety profile and tolerability seem to be equivalent to those observed with placebo and, so far, no clear class-specific adverse effects have been attributed to the ARBs. In addition, they are reportedly organ protective. Several randomized clinical trials of ARBs in patients with hypertension demonstrated that the ARBs offer clinical benefits in patients with heart failure, post–myocardial infarction, atrial fibrillation and diabetic nephropathy in addition to their blood pressure (BP)-lowering effects. Furthermore, ARBs have positive effects in reducing inflammation and improving adipose tissue metabolism.[1]

Fimasartan (BR-A 657, 2-n-butyl-5-dimethylaminothiocarbonylmethyl- 6-methyl-3{[2=-(1H-

tetrazol-5-l) biphenyl- 4-yl] methyl}, pyrimidin-4(3H); is a new non-peptide angiotensin II receptor blocker with a selective AT1– receptor blocking effect.[2]

Fimasartan safety profile and pharmacokinetic and pharmacodynamic characteristics in healthy volunteers have been well characterized.[3] It is also reportedly tolerable when used in combination with hydrochlorothiazide, amlodipine, or digoxin in healthy volunteers.[4,5,6] However, its efficacy and tolerability in hypertensive patients have not been documented in therapeutic exploratory clinical studies or compared with other ARBs. Angiotensin II is the most important molecule in the renin-angiotensin system. Angiotensin II increases heart contractions and sodium reabsorption and has harmful effects on organs and vessels due to vascular hypertrophy and vasoconstriction. Restricting the effects of angiotensin II is not only effective in decreasing blood pressure (BP) but also has positive effects in preventing and improving heart failure, renal failure, stroke, and diabetic renal neuropathy. Fimasartan chemical structure shows a bio-isosteric replacement of the imidazole part of Losartan with pyrimidin-4(3H)-one that provided higher potency and stronger efficacy than Losartan and exhibited a quick onset of antihypertensive effect during initial Phase II and III clinical trials. Fimasartan, the ninth ARB developed, has minimal side effects, high overall patient compliance, and an evident effect on decreasing BP. Collectively, Fimasartan leads to a reduction in blood pressure and alleviation of hypertensive symptoms. ARBs like Fimasartan have also shown to be protective against stroke, myocardial infarction, and heart failure. Fimasartan has been shown to reduce cardiac hypertrophy, fibrosis, remodeling, and unnecessary cell proliferation via blockage of AT1 activation conceivably through decreased Endothelin 1 production, a result of AT1 activation. Fimasartan can also block TGF-β1 production (also AT1 dependent), which contributes to fibrosis and AT1 activation conceivably through decreased Endothelin 1 production, a result of AT1 activation. Fimasartan can also block TGF-β1 production (also AT1 dependent), which contributes to fibrosis and ventricular damage post-infarct.[7] In clinical trials, Fimasartan was well tolerated in all patients.

The objective of current study is to evaluate efficacy safety and tolerability of Fimasartan vs. Losartan in patients of Mild Essential Hypertension. Losartan was used as a comparator because it is not only first ARB to be marketed but also one of the most widely used ARB after generic form was made available.

MATERIAL AND METHODOLOGY

Study design

This study was a comparative, randomized, double blind, parallel group and non-crossover multi-centric clinical study conducted between Oct 11, 2017 to May 10, 2018 in 13 centers across India in subjects suffering with Mild Essential Hypertension.

All procedures followed the tenets of the Declaration of Helsinki, were in accordance with all regulatory standards, were approved by an Institutional Review Board and all subjects signed an informed consent form. Protocols and Inform consent were approved by Indian Regulatory authority and Institutional Ethical Committee.

Subjects

206 subjects both male and female subjects suffering from Mild essential hypertension were included in the study for the duration of 90 days. They were randomized (simple block randomization) by computer generated system to either of the study arms in 1:1 proportion (Test: Reference).

Study Eligibility Criteria

Subjects (Male & Female) aged between 18-65 years diagnosed with newly diagnosed treatment naïve with Hypertension with SBP 140 to 159 mmHg and DBP 90 to 99 mmHg (measured by Accredited Automated Sphygmomanometer in sitting position, 3 readings taken at a difference of 10 minutes and the average of 3 readings was considered for the eligibility criteria) Also Voluntary willingness of patients to give written informed consent prior to participation in clinical trial was undertaken.

Subjects with Moderate to Severe Hypertension, any other antihypertensive or diuretic drugs, severe renal impairment (eGFR ≤ 30ml/min), Type I or Type II Diabetes Mellitus, hepatic impairment, structural heart disease like hypertrophic obstructive cardiomyopathy, hemodynamically significant aortic valve or mitral valve disease, Pericardial disease were excluded from the study. Other exclusion criteria was subjects who are on any other antihypertensive or diuretic drugs. Serum potassium > 5.5 mEq/L or < 3.0 mEq/L at baseline. Patients with history of wasting disease, autoimmune disease, connective tissue disease or History of drug or alcohol abuse within the previous 2 years. Any confirmed diagnosis of cancer, confirmed HIV, Hepatitis B or C. Pregnant or lactating women or women with child bearing potential who are not taking acceptable form of contraceptive. Known or suspected hypersensitivity to any drug that will be administered during the study.

Treatment and Compliance

Both test and reference product formulations were administered as one tablet once daily of Fimasartan or Losartan in the morning, possibly at the same time every day. Duration of participation in the study for each patient was planned to be 90±2 days.

The compliance was observed through drug accountability and subject diary. Adherence to assigned regimen was assessed by recording the amount of returned investigational products at the end of study treatment. Treatment compliance was considered

adequate, when provided patients have used at least 75% of scheduled doses.

Time and Events Schedule

There were 6 visits in the study such as Screening Visit, Baseline/ Randomization Visit (Day 0), Visit 2 (Day 7), Visit 3 (Day 15) and Visit 4(Day30) Visit 5(Day 60) and Final Visit (day 90). The study medication either Fimasartan tablet or Losartan Tablet were handed over to randomized subjects on Day '0' (Visit - 1) as per randomization schedule and instructed for their direction of use.

Demographical variables (age, sex, race, height and weight), medical history, physical examination including vital signs and electrocardiogram (ECG) was done at every visit laboratory investigations such as haematology and blood chemistry, were performed at both screening and final visit (Day 90). Assessment of primary and secondary efficacy parameters and Systolic and Diastolic BP measurements observations were recorded on baseline visit to each follow up visit. Ambulatory BP measurements were done Visit 3 (day 15) and Visit 6 (day 90).

Efficacy and Safety Parameters

Primary Efficacy parameter

Evaluation of mean reduction in the sitting clinic SBP and DBP from baseline to Day 90 (±2) after 10 minutes rest period, mean reduction in ABPM Parameters from baseline to Day 90 (±2) (Mean 24hour SBP and DBP, Mean Day Time SBP and DBP, Mean Night Time SBP and DBP) were done to evaluate of efficacy Fimasartan tablet.

Secondary Efficacy Parameter

Mean change in Heart Rate from baseline to end of study

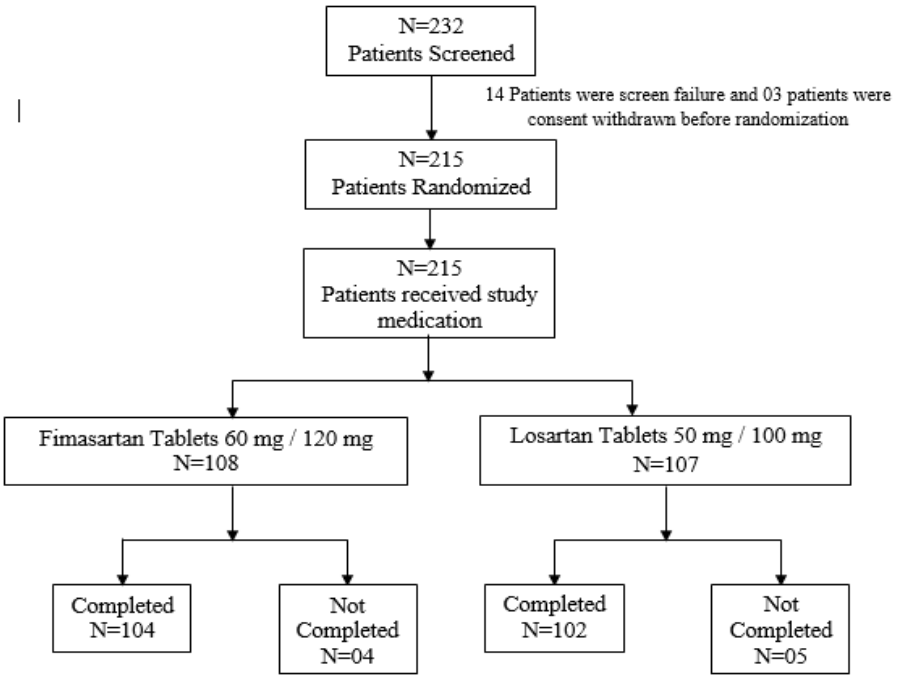
Adverse Events (AEs) and Serious Adverse Events (SAEs) were summarized by counting both the number of separate events and the number of subjects experiencing any of these events during the study period was recorded. Furthermore, similar summaries were provided and stratified according to the seriousness, severity and relationship to the study medication.

Statistical methods

Statistical analysis was done using SAS 9.4. Continuous variables were statistically tested using Two-sample t-test. Categorical variables were tested using Chi-square test. Primary efficacy analysis was done using Two-sample t-test and Wilcoxon signed rank sum test. Secondary efficacy analysis was done using Two-sample t-test and Wilcoxon signed rank sum test. All safety parameters were analyzed using Wilcoxon signed rank sum test, Two-sample t-test and descriptive statistics.

RESULTS

Total of 232 patients were screened out of which 215 patients were randomized in the study. 14 patients were screen failure while 03 patients were consent withdrawn before randomization. 03 patients were lost to follow-up, 04 patients were consent withdrawn after randomization and 01 patient was discontinued from the study. Total 108 patients were randomized in test arm i.e. Fimasartan Tablets 60 mg / 120 mg and 107 patients were randomized in reference arm i.e. Losartan Tablets 50 mg / 100 mg. None of the patient was terminated from the study for any adverse event as per the protocol. Total 104 patients in the test arm and 102 patients in the reference arm completed the study. Following figure shows the summary of the patient disposition in the study.



EFFICACY ANALYSIS

Efficacy of the investigational product was analyzed on the basis of Mean reduction in the sitting clinic SBP from baseline to Day 90 (±2) after 10 minutes rest period, Mean reduction in the sitting clinic DBP from baseline to Day 90 (±2) after 10 minutes rest period, Mean reduction in ABPM Parameters from baseline to Day 90 (±2) (Mean 24hour SBP and DBP, Mean Day Time SBP and DBP, Mean Night Time SBP and DBP) and Mean change in Heart Rate from baseline (Day 0) to end of the study (Day 90 (±2)). As per the statistical analysis plan, the efficacy data was analyzed for effect on individual and cumulative efficacy parameter.

PRIMARY EFFICACY PARAMETER

1. Mean Change from baseline in sitting SBP

Table 1: Mean Change from baseline in sitting SBP.

Visit	Statistics	Fimasartan Tablets 60 mg /120 mg (n/N)	Losartan Tablets 50 mg / 100 mg (n/N)	P-value
Visit 1 / Baseline	N	108	107	0.25 (-1.518, 2.0283)
	Mean (SD)	149.29 (4.35)	150.22 (4.80)	
Visit 6	N	104	102	
	Mean (SD)	134.81 (5.80)	136.31 (6.15)	
Change from Baseline to Visit 6	N	104	102	
	Mean (SD)	14.48 (6.00)	13.91 (6.89)	
	95% CI (Lower CI, Upper CI)	(23.324, 25.657)	(22.883, 25.588)	
	Mean (95% CI)			
	P-value within Treatment	0.0001	0.0001	
	P-value between Treatment			0.7770

Note: *P*-value is obtained using Two-sample t-test to compare change from baseline values of Fimasartan Tablets 60 mg /120 mg and Losartan Tablets 50 mg / 100 mg.
P-value within Treatment obtained using paired t-test.

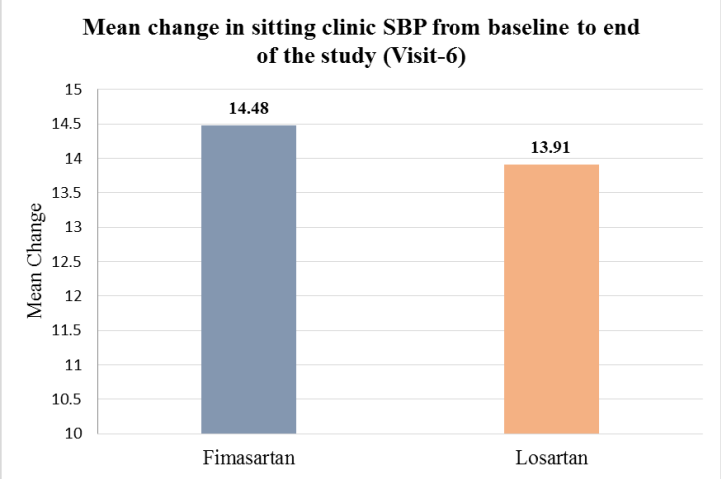


Figure 1: Mean change in sitting clinic SBP from baseline to end of the study (visit-6).

2. Mean Change from baseline in sitting DBP

Table 2: Mean Change from baseline in sitting DBP.

Visit	Statistics	Fimasartan Tablets 60 mg /120 mg (n/N)	Losartan Tablets 50 mg / 100 mg (n/N)	*P*-value
Visit 1/ Baseline	n	108	107	0.65 (-0.668, 1.9852)
	Mean (SD)	92.36 (3.60)	92.55 (3.54)	
Visit 6	n	104	102	
	Mean (SD)	82.90 (3.96)	83.76 (3.93)	
Change from Baseline to Visit 6	n	104	102	
	Mean (SD)	9.46 (5.14)	8.79 (4.49)	
	95% CI (Lower CI, Upper CI)	(12.405, 14.403)	(11.863, 13.627)	
	Mean (95% CI)			
	P-value within Treatment	0.0001	0.0001	
	P-value between Treatment			0.3286

Note: *P*-value is obtained using Two Sample t-test to compare change from baseline values of Fimasartan Tablets 60 mg /120 mg and Losartan Tablets 50 mg / 100 mg.
P-value within Treatment obtained using paired t-test.
Note: *P*-value is obtained using Two Sample t-test to compare change from baseline values of Fimasartan Tablets 60 mg /120 mg and Losartan Tablets 50 mg / 100 mg.
P-value within Treatment obtained using paired t-test.

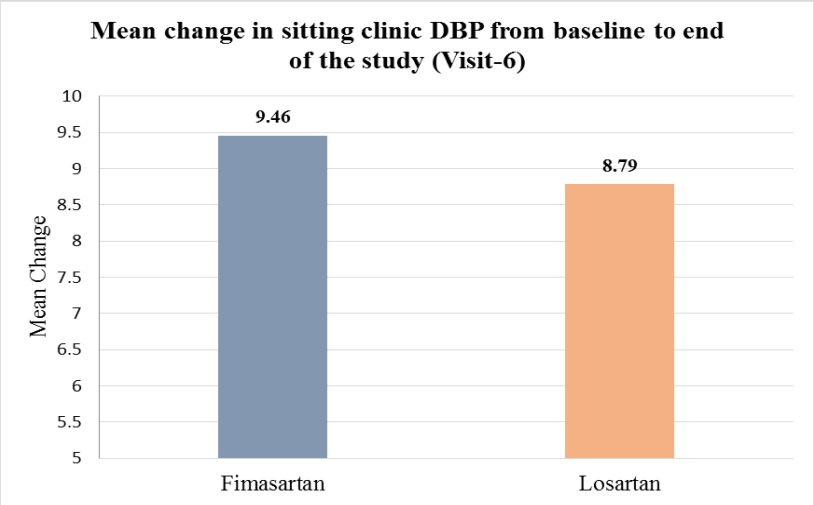


Figure 2: Mean change in sitting clinic DBP from baseline to end of the study (visit-6).

3. Mean Change from baseline in 24 hour ABPM SBP

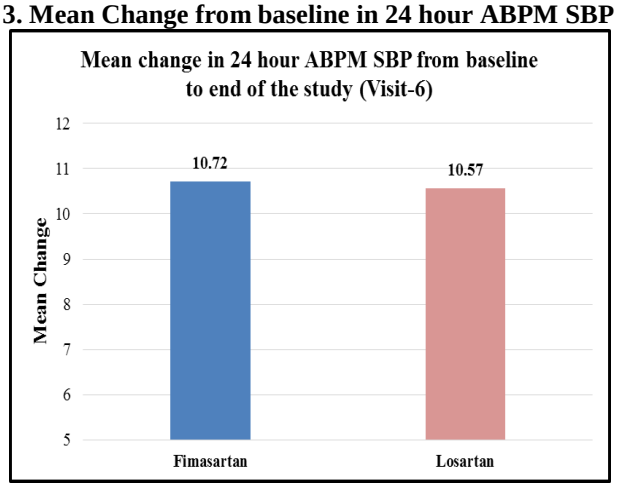


Figure 3: Mean change in 24 hour ABPM SBP from baseline to end of the study (visit-6).

4. Mean Day Time ABPM DBP

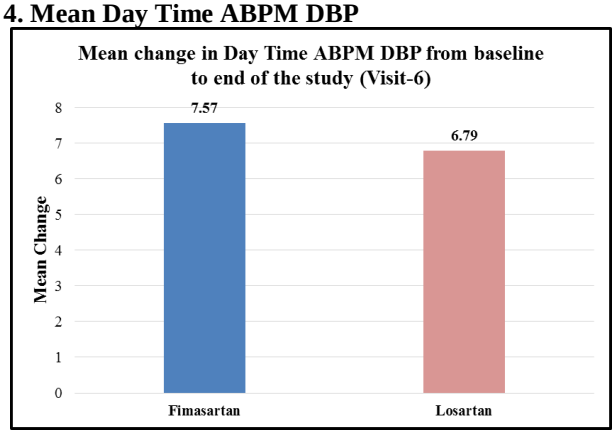


Figure 4: Mean change in Day Time ABPM DBP from baseline to end of the study (visit-6).

5. Mean Night Time ABPM SBP

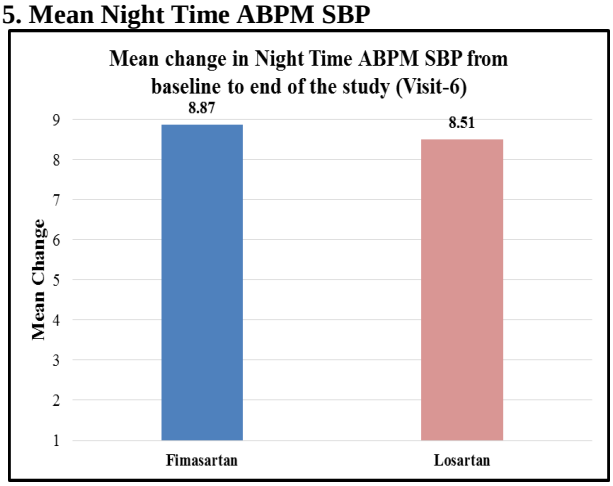


Figure 5: Mean change in Night Time ABPM SBP from baseline to end of the study (visit-6).

6. Mean Night Time ABPM DBP

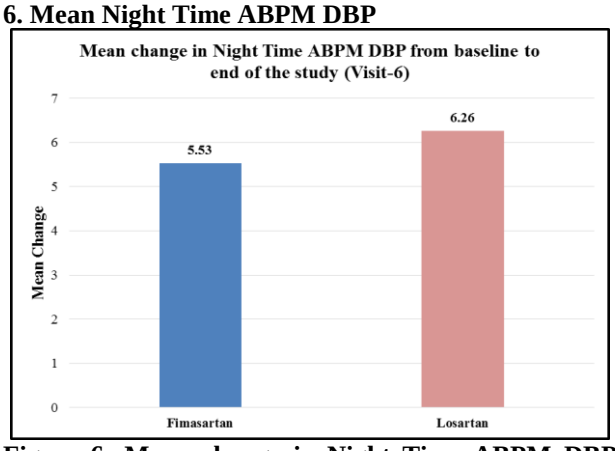


Figure 6: Mean change in Night Time ABPM DBP from baseline to end of the study (visit-6).

SECONDARY EFFICACY PARAMETER

A) Heart Rate

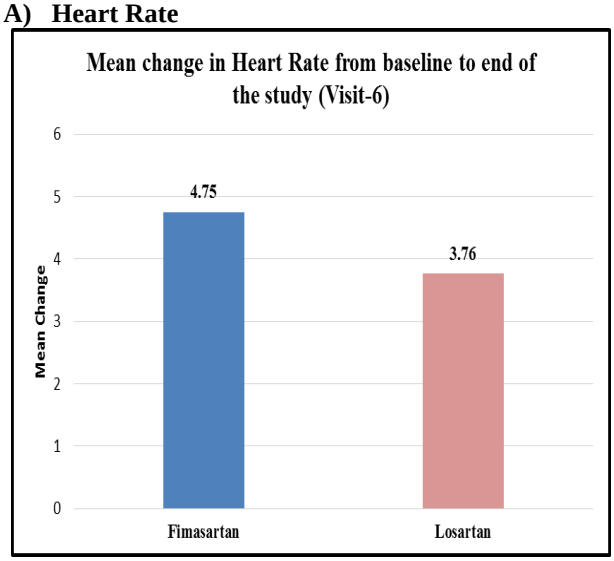


Figure 7: Mean change in Heart Rate from baseline to end of the study (visit-6).

Dose Escalation by Treatment Group

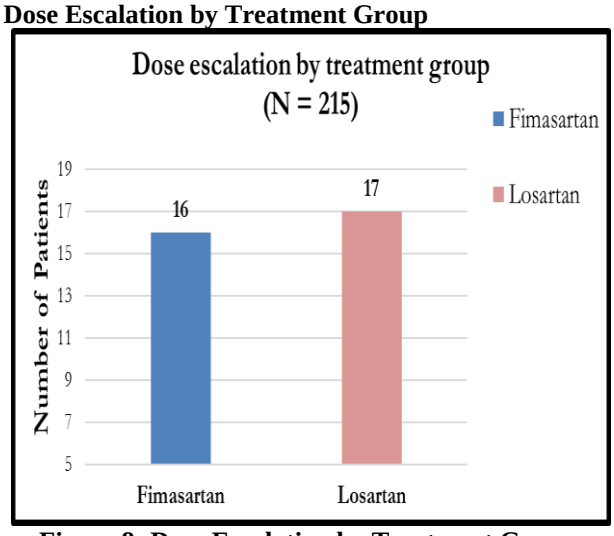


Figure 8: Dose Escalation by Treatment Group.

Note: For subjects who did not show a reduction in the blood pressure (i.e the DBP ≥ 90 mmHg and SBP ≥ 140 mmHg) at Visit 3, Day 15, then the dose was increased to double.

SAFETY AND TOLERABILITY EVALUATION

There were 19 clinical adverse events reported in 18 patients. The adverse events were Abdominal Pain, Headache, Diarrhea, Itching in Skin, Nausea, Gastritis, Fever, Anaemia, Urinary Tract Infection, etc. All the adverse events were followed up until they were completely resolved. No adverse event led to serious adverse event.

The patients experienced adverse events which include Abdominal Pain, Headache, Diarrhea, Itching in Skin, Nausea, Gastritis, Fever, Anaemia, Urinary Tract Infection, etc. All the AEs were mild in nature. None of the AEs from Fimasartan Tablets 60 mg / 120 mg arm were related to IP and none of the AEs from Losartan Tablets 50 mg / 100 mg arm were related to IP. There was no mortality or hospitalization reported in both arms throughout trial period.

DISCUSSION

This Randomized, Double Blind, Multicentric, Active Controlled, Parallel Group, Two Arm, Phase III Clinical Trial assessed the Efficacy, Safety and Tolerability of Fimasartan Tablets Vs. Losartan Tablets in Patients with Mild Essential Hypertension.

We found that Fimasartan Tablets was shown to be non-inferior when compared with Losartan Tablets in primary efficacy and secondary efficacy parameters. Fimasartan Tablets was shown to be comparable safety profile with Losartan Tablets. Results of our study was similar to obtained in previous study of Sang Eun Lee, MD et all carried out in 506 patients of essential Hypertension . In this study, Fimasartan 60/ 120 mg with optional titration was noninferior to losartan 50/100 mg. By post hoc analysis of the between group difference, the data suggest that Fimasartan 60/ 120 mg was also superior to losartan 50/100 mg with optional titration in terms of lowering BP as measured by siDBP. The results of this study suggest that Fimasartan 60/120mg once daily with optional titration was noninferior to losartan 50/100 mg once daily with optional titration in controlling BP for 12 weeks in eligible Korean patients with mild-to-moderate hypertension.[1]

Accumulated data for fimasartan use in close to 20,000 patients is available. Fimasartan was found to have an excellent efficacy and tolerability profile in a large-scale observational population study - Safe-KanArb. In this study, a total of 14,151 patients with mean age of 59 ± 12 years were evaluated. This study established the safety, efficacy, and compliance of this molecule. The Systolic blood pressure (SBP) fell by an average of - 18.65 mm of Hg and Diastolic blood pressure by - 9.73 mm of Hg with drug therapy at 2 months. Interestingly, the pulse rate declined from 74.4 to 71.9 beats per min in the treatment arm. The benefits were attained irrespective of age, sex, comorbidities and background antihypertensive therapy. It should be noted that more than half of the study population (63%) was on background anti-hypertensive therapy underscoring the potency and efficacy of the drug. The drug was found to be excellent in patients potentially at higher risk for adverse events.[8]

The K-MetS study of 10601 patients was planned to evaluate long-term effects of fimasartan on major adverse cardiovascular outcomes. The study also evaluated long-term metabolic effects of fimasartan. Three-year follow-up was planned in this study. At 1-year follow-up, in a sub group analysis published in 2017, fimasartan significantly decreased the albumin/creatinine ratio. The systolic blood pressure fell from 143.7 ± 17.2 mm of Hg to 126.7 ± 12.6 mm of Hg at 1 year (a fall of around 17 mm of Hg). On a similar

note, the diastolic BP decreased from 88.4 ± 11.48 at baseline to 78.6 ± 8 mm of Hg. Waist circumference and triglyceride levels were also diminished simultaneously.[9]

In another study, the drug was associated with reduction in day to day BP variability independent of absolute BP reduction.[10]

Fimasartan was similarly effective in reducing systolic as well as diastolic BP in hypertensive elderly patients compared with nonelderly patients in a sub group analysis of K-MetS study. It also resulted in better pulse pressure reduction with similar home blood pressure reduction efficacy and safety in hypertensive elderly patients.[11]

Lee et al conducted a study, where Fimasartan 60mg or 120mg was compared to Valsartan 80mg for 8 weeks. Once-daily Fimasartan effectively maintained a BP-reduction profile over the full 24-hour dosing interval; this profile was comparable to or slightly better than that of once-daily valsartan. Fimasartan was well tolerated; headache was the most common adverse event.[12]

Ye Seul Yang evaluated Forty-one patients for Blood pressure, HbA1c, and oral glucose tolerance (OGTT parameters in this open-labeled, active comparator-controlled and crossover study and found, compared to amlodipine, Fimasartan increased late-phase glucose-stimulated insulin secretion in patients with type 2 diabetes and hypertension.[13]

In the current study, Fimasartan and Losartan were comparable is safety evaluation The adverse events were Abdominal Pain, Headache, Diarrhea, Itching in Skin, Nausea, Gastritis, Fever, Anaemia, Urinary Tract Infection, etc. All the adverse events were followed up until they were completely resolved. No adverse event led to serious adverse event.

CONCLUSION

Hypertension is a chronic disease and requires long term treatment. The results of the present study suggest that Fimasartan 60/120 mg once daily was noninferior to losartan 50/100 mg once daily in controlling BP for 12 weeks in eligible Indian patients with mild-to-moderate hypertension. The differences in their tolerability did not reach the level of statistical significance, and both drugs were well tolerated. Furthermore, this efficacy and tolerability were maintained throughout the additional 12-week extension study. Fimasartan can be considered as a potential treatment option for patients with Essential Hypertension

REFERENCES

1. Sang un Lee, MD et al. Clinical Therapeutics/Volume 34, Number 3, 2012 Efficacy and Tolerability of Fimasartan, a New Angiotensin Receptor Blocker, Compared With Losartan (50/100 mg): A 12-Week, Phase III, Multicenter, Prospective, Randomized, Double-Blind, Parallel-Group, Dose Escalation Clinical Trial With an Optional 12-Week Extension Phase in Adult Korean Patients With Mild-to-Moderate Hypertension.
2. Sohn YT. Crystal forms of an angiotensin II receptor antagonist BRA657. J Therm Anal Calorim, 2007; 89: 799– 802.
3. Chi YH, Lee H, Paik SH, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of fimasartan following single and repeated oraladministration in the fasted and fedstates in healthy subjects. *Am J Cardiovasc Drugs*, 2011; 11: 335–346.
4. Yi S, Kim JW, Kim TE, et al. Effect ofmultiple doses of fimasartan, anangiotensin II receptor antagonist, on the steady-state pharmacokinetics of digoxin in healthy volunteers. *Int J Clin Pharmacol Ther*., 2011; 49: 321–327.
5. Yi S, Kim TE, Yoon SH, et al. Pharmacokinetic interaction of fimasartan, a new angiotensin II receptor antagonist, with amlodipine in healthyvolunteers. *J Cardiovasc Pharmacol*, 2011; 57: 682–689.
6. Jeon H, Lim KS, Shin KH, et al. Assessment of the drug-drug interactionsbetween fimasartan andhydrochlorothiazide in healthy volunteers. *J Cardiovasc Pharmacol*, 2012; 59: 84 –91.
7. Je Hak Kim Fimasartan, a Novel Angiotensin II Receptor Antagonist Arch Pharm Res, 2012; 35(7): 1123-1126.
8. Park JB, Sung K-C, Kang SM, Cho EJ. Safety and efficacy of fimasar-tan in patients with arterial hypertension (Safe-KanArb Study) Am J Cardiovasc Drugs, 2013; 13: 47-56.
9. Park JB, Kim S-A, Sung K-C, Kim JY. Gender-specific differences in the incidence of microalbuminuria in metabolic syndrome patients after treatment with fimasartan: The K-MetS study. PLoS One, 2017; 12: e0189342.
10. Shin MS, Kang DR, Kim C, Cho EJ, Sung KC, Kang SM, *et al*. Fimasartan for independent reduction of blood pressure variability in mild-to-moderate hypertension. Drug Des Devel Ther., 2016; 10: 1573-80.
11. Cho EJ, Sung KC, Kang SM, Shin M-S, Joo SJ, Park JB. Fimasartan reduces clinic and home pulse pressure in elderly hypertensive patients: A K-MetS study. PLoS One, 2019; 14: e0214293.
12. Lee HY, Kim CH, Song JK, Chae SC, Jeong MH, Kim DS, *et al*. 24-Hour blood pressure response to lower dose (30 mg) fimasartan in Korean patients with mild to moderate essential hypertension. Korean J Intern Med., 2017; 32: 1025-36.
13. Yang YS, Lim MH, Lee SO, Roh E, Ahn CH, Kwak SH, *et al*. Fimasartan increases glucose-stimulated insulin secretion inpatients with type 2 diabetes and hypertension compared with amlodipine. Diabetes Obes Metab, 2018; 20: 16707.