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Metoprolol succinate extended-release in treating high blood pressure-A post-marketing surveillance study

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A B S T R A C T

Background: Hypertension increases the incidence of congestive heart failure, myocardial infarction, and ischemic stroke. In previous studies, metoprolol succinate extended release (XL) has been identified as a plausible antihypertensive medication compared to others. Apart from angiotensin II receptor antagonists, this β-blocker effectively reduces mortality and hospitalisation rate due to cardiovascular accidents. **Aim:** The aim was to identify the impact of metoprolol succinate XL 50/100mg on hypertensive patients for 3 months as part of a post-market surveillance study involving the African population. **Methods:** Out of 200 patients, a total of 184 patients were enrolled on the study. **Results:** Metoprolol succinate XL led to a significant decrease in the mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP), and mean heart rate (HR) at 4th, 8th, and 12th-week from baseline ($p<0.0001$). 39.50%, 18%, 61.50%, and 45.50% of patients went from Grade 1 to normal, Grade 2 to Normal, High Normal to Normal and isolated systolic hypertension to Normal categories of BP, respectively. Large effect size was noticed in analyses, as estimated by Cohen's d-value, which implied a practical significance of using the drug in the study population with respect to lowering BP and HR. Mean SBP, DBP, and HR change was higher in the baseline to 4-week, 8-week, and 12-week groups compared to inter-weekly changes. Moreover, mean baseline SBP and DBP were higher in groups administered with 50mg of the drug. **Conclusion:** These findings suggest that metoprolol succinate XL 50/100mg significantly lowers mean BP and HR among African hypertensive patients.

Keywords: Metoprolol succinate, extended-release, hypertension, systolic, diastolic, heart rate

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CONTENTS

1. Introduction

Hypertension has inflicted menaces on human lives by raising the chances of cardiovascular diseases, chest pain (angina), heart failure, stroke or cerebrovascular diseases, with an estimated prevalence of 1.28 billion population worldwide in 2021 (World Health Organization, WHO), mostly living in the low-and middle-income countries [1]. The increasing burden of hypertension and hypertension-induced cardiovascular diseases has accelerated the discovery of several antihypertensive medications showing higher efficacies with reduced complications [2]. In addition to antihypertensive agents, which target the action of angiotensin II of the renin-angiotensin-aldosterone-system (RAAS) through inhibition of angiotensin II receptor (AT_1), β-blockers have emerged as an effective therapy in mitigating cardiovascular events and mortality among patients with hypertension, tachycardia or congestive heart failure [3]. Recent advancement in the formulation of metoprolol succinate extended-release (Met XL) has provided a relatively stable plasma concentration to metoprolol with retention of pharmacokinetic and pharmacodynamic properties after once-daily administration. Apart from that, its β-antagonistic property minimises the cardiac output through negative ionotropic and chronotropic effects, reduces oxygen demand and promotes vasodilation by inhibiting total peripheral resistance. Metoprolol succinate has been developed as a selective β-blocker agent competitively inhibiting the action of catecholamine through the interaction with β-adrenergic receptors, which exhibited antiarrhythmic and anti-ischemic effects, lipid solubility, pharmacokinetic profile, and potential benefits with respect to a decrease in inflammation, stress, endothelial dysfunction, heart rate, and risk of plaque rupture, with evidence of no intrinsic sympathomimetic activity (ISA) [4-7]. Furthermore, according to the MERIT-HF study, metoprolol succinate extended-release in combination with standard therapy reduced the incidence of hospital admission due to worsening of heart failure in left ventricular systolic dysfunction and ameliorates survival while uplifting the well-being of patients [8,9]. Incidentally, a high CRP level enhances the likelihood of developing cardiovascular complications and hence, is observed at an elevated level among hypertensive patients or patients experiencing congestive heart failure. In a 3-month long clinical trial for the treatment of uncontrolled hypertension, researchers observed a significant decline in mean CRP level with metoprolol succinate extended-release at a higher dose [10]. These findings led to the establishment of metoprolol succinate extended-release as a potent antihypertensive therapy for treating congestive heart failure, cardiovascular disease, angina, or cerebrovascular accident patients following its approval from the FDA. To our information, this was the first study conducted with metoprolol succinate in the west African population. In addition, this study has helped us understand the real world clinical effects of Metoprolol XL 50/100 mg among hypertensive patients and identify whether metoprolol retains its observation from premarketing trials.

2. Material and methods

Data Collection: SEAM (Safety and Efficacy Assessment of Metoprolol extended-release tablet), a prospective, observational, open label, multi-centric, post-marketing surveillance study across countries in West Africa and Central Africa, was conducted to document the real-time experience of the Metoprolol Succinate extended-release tablet (Met XL of Ajanta Pharma) in an African population. The study initially planned to recruit 300 patients; however, a total of 200 patients enrolled between May 2019 and Sep 2020.

Patient profiling: Interested patients ≥ 18 years of age suffering from uncontrolled hypertension with/without co-morbidities were considered for inclusion in the study. Patients having a prior history of compromised renal/hepatic function, systemic lupus erythematosus, and pregnant or lactating patients were excluded from the study.

Methodology: A predesigned structured proforma was used to obtain information from the prescribing physicians regarding the efficacy and safety of the Metoprolol Succinate extended-release tablet. Demographic characteristics, including Systolic Blood Pressure [SBP], Diastolic Blood Pressure [DBP] and Heart Rate [HR], and Laboratory investigations of patients were compared at baseline before starting Metoprolol Succinate extended-release tablet and at the end of 3 months of therapy. Depending on the severity of hypertension, all the patients have been categorised into different hypertension grades as grade 1, grade 2, high-normal, isolated systolic hypertension, and normal based on the latest guidelines by the International Society of Hypertension, 2020. Grades were defined as follows: normal – < 130 mmHg SBP and < 85 mmHg DBP; high normal – 130-139 mmHg SBP and/or 85-89 mmHg DBP; Grade 1 – 140-159 mmHg SBP and/or 90-99 mmHg DBP; Grade 2– >160 mmHg SBP and/or > 100 mmHg DBP; isolated systolic hypertension – ≥140 mmHg SBP and < 90 mmHg DBP. Grading was done at visit 1 and at the end of 3 months of therapy (visit 12). The prescriber's perception of the overall global efficacy and global safety of the Metoprolol Succinate extended-release

tablet was also captured based on a 4-point rating (Excellent, Good, Fair and Poor).

Dosing regimen: Metoprolol Succinate extended-release tablets (50/100 mg) were administered orally with liquid and with or without food once daily. However, it was not recommended to be administered in the presence of contraindications as per prescribing information.

Primary Endpoint: The primary efficacy endpoint analysed the mean change in SBP, DBP and HR at 4-week, 8-week and 12-week treatment from baseline (week 0).

Secondary Endpoint: The secondary safety endpoint attempted to detect and compare the possible adverse events between groups throughout the 3-month treatment course.

Statistical analysis: Descriptive statistics identified a total number of patients with SBP, DBP, and HR showing standard deviation, standard error, and their mean distribution of SBP, DBP, and HR at baseline and after 3-month of metoprolol succinate XL at 50/100 mg daily dosage regimens. Mean changes in SBP, DBP, and HR at 4, 8, and 12 weeks were compared using a two-tailed student's t-test and paired t-test at a 0.05 level of significance to detect the impact of metoprolol succinate extended-release 50/100 mg dosage on patients. An effect size of the medication was estimated by Cohen's d value which defines the relationship between variables or the difference between groups, suggesting the practical significance of the PMS study on hypertensive patients in the African population. According to Cohen's d value, a value of 0.2 indicated a small effect size with limited practicality, whereas values ≥ 0.8 were suggestive of a large effect size showing the practical significance of the study.

Samples were grouped according to their age, dosage regimens of either 50 mg or 100 mg metoprolol succinate XL at baseline and compared for the effect of dosages on SBP, DBP, HR, and age by logistic regression analysis in independent sample tests. Additionally, the Chi-square test generated the Pearson Chi-square test, likelihood ratio, and linear-by-linear association. The statistical analyses were done using the Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS Inc., Chicago, Illinois, USA) software.

3. Results

Demographic characteristics: Out of the total 200 patients, 184 (92%) patients comprising 94 females (51.09%) and 90 males (48.91%), underwent the study with metoprolol succinate extended release 50/100 mg dosage regimens. At baseline, these 184 patients represented a mean age (mean age ± SD) of 51.80 ± 14.82, mean SBP of 155.658 ± 20.0929 mmHg, mean DBP of 92.777 ± 11.5242 mmHg, and mean HR of 104.495 ± 18.554 (Table 1). A total of 62 patients (33.7%) and 80 patients (43.48%) presented evidence of less than 1 year and 1-10 years of disease history, respectively, whereas only 10 patients (5.43%) reported more than 10 years of disease history. In addition, HBP and tachycardia were reported among 124 patients (67%) and 48 patients (25.9%), respectively. Furthermore, co-morbidities were observed only among 82 patients (44.57%). Metoprolol succinate XL 50 mg was consumed by 138 patients (75%), and 46 patients (25%) received the 100 mg dosage regimen of metoprolol succinate extended release (Table 1).

Table 1: Baseline characteristics of patients

Gender	Frequency	Percent
Female	94	51.09
Male	90	48.6
Total	184	100.0
Diagnosis	**Frequency**	**Percent**
HBP	123	66.85
Tachycardia	48	26.09
Other	13	7.07
Total	184	100.0
Duration of illness	**Frequency**	**Percent**
Less than One year	62	33.70
1-10 years	80	43.48
Greater than 10 years	10	5.43
Don't know	32	17.39
Total	184	100.0
Comorbidities	**Frequency**	**Percent**
No	102	55.43
Yes	82	44.57
Total	184	100.0
Metoprolol	**Frequency**	**Percent**
50 mg	138	75
100 mg	46	25
Total	184	100.0

*HBP= High Blood Pressure

At visit 1, all the patients were categorised into different hypertension grades according to the severity of their hypertension. Among the 184 patients who were available for evaluation, 44 patients (23.91%) were in the grade 1 category, 73 patients (39.67) in the grade 2 category, 14 patients (7.61%) in the high-normal category, 39 patients (21.20%) in the isolated systolic hypertension category, and 14 patients (7.61%) in the normal category. Out of 184 patients, only 156 completed the 3 months study; hence the data for grades of hypertension at week 12 is available for only these patients. At week 12, grades of hypertension for patients were as follows: 2 patients (1.30%) in grade 1,

84 patients (53.80%) in high normal grade, 11 patients (7.10%) in isolated systolic hypertension category, and 59 patients (37.80%) in the normal category. Among the 38 patients in grade 1 at visit 1, 22 (57.90%) were in the high normal category, while 15 (39.50%) were normal at visit 12. Among the 61 patients in grade 2 at visit 1, 2 patients (3.30%) remained in grade 1, while 39 patients (63.90%) were in the high normal category, 9 patients (14.80%) in the isolated systolic hypertension category, and 11 patients (18.00%) were in normal category at visit 12. Among the 13 patients in the high-normal category at visit 1, 5 patients (38.50%) were in the high normal category, whereas 8 patients (61.50%) were in the normal category at visit 12. Among the 33 patients in the isolated systolic hypertension category at visit 1, 17 patients (51.50%) were in high normal grade, 1 patient (3.00%) in the isolated systolic hypertension category, and 15 patients (45.50%) in the normal category at visit 12. Lastly, among the 11 patients in the normal category at visit 1, 1 patient (9.10%) was in the high normal category, and 10 patients (90.90%) were in the normal category at visit 12. These results show that metoprolol succinate extended-release tablets effectively reduced the severity of hypertension.

According to the global efficacy 4-point rating scale, 79.35% of patients exhibited excellent outcomes, and 9.78% were observed with good outcomes following metoprolol succinate extended-release administration (Table 2). As per the safety and tolerability rating scale, 84.24% (155/184), 4.89% (9/184), and 0.54% (1/184) of patients were identified with excellent, good, and poor outcomes, respectively. However, 10.33% (19/184) of patients could not be detected with any of these outcomes.

Table 2: Overall efficacy and tolerability of patients with metoprolol dosage regimens

Efficacy	Frequency	Percent	Tolerability	Frequency	Percent
Poor	1	0.54	Poor	1	0.54
Good	18	9.78	Good	9	4.89
Excellent	146	79.35	Excellent	155	84.24
Don't know	19	10.33	Don't know	19	10.33
Total	184	100.0	Total	184	100.0

Primary endpoint:

The study demonstrated a significant decline in the mean SBP after metoprolol succinate extended-release 50/100 mg administration at 4-week with evidence of large effect size as per Cohen d value (> 0.8) (mean change: 16.57 ± 13.18 mmHg, t = 16.542, df = 172, 95% CI = 14.59-18.55, p< 0.0001, Cohen d: 0.8591). The mean SBP changed significantly from baseline to 8-week (mean change: 23.19 ± 14.91 mmHg, t = 19.42, df = 155, 95% CI = 20.83-25.55, p< 0.0001, Cohen d = 1.26) and baseline to 12-week (mean change: 25.39 ± 15.81 mmHg, t = 20.05, df = 155, 95% CI = 22.89-27.89, p< 0.0001, Cohen d = 1.38) with metoprolol succinate extended-release (Table 3, figure 1).

The drug was able to significantly lower mean DBP from 92.48 ± 11.02 mmHg at baseline to 81.99 ± 9.79 mmHg at 4-week (mean change: 10.49 ± 10.50 mmHg, t = 13.17, df = 173, 95% CI = 8.92-12.06, p< 0.0001, Cohen d = 0.95) retaining the observation with respect to Cohen d value. Following administration of the drug, mean DBP also significantly declined at 8-week and 12-week observations by 13.20 ± 11.74 mmHg (t = 14.045, df = 155, 95% CI = 11.34-15.06, p< 0.0001, Cohen d = 1.21) and 15.80 ± 12.11 mmHg (t=16.29, df = 155, 95% CI = 13.89-17.72, p< 0.0001, Cohen d = 1.45) (Table 4, figure 1). Mean HR appeared significantly lower at 4-week (mean change: 23.04 ± 14.59 mmHg, t = 20.76, df = 172, 95% CI = 20.85-25.23, p< 0.0001, Cohen d = 1.22), 8-week (mean change: 27.26 ± 15.03 mmHg, t = 22.64, df = 155, 95% CI = 24.88-29.64, p< 0.0001, Cohen d = 1.41), and at 12-week (mean change: 29.31 ± 12.11 mmHg, t = 16.29, df = 155, 95% CI = 13.89-17.72, p< 0.0001, Cohen d = 1.52) compared to baseline blood pressure of patients (Table 5, figure 2). In addition to that, mean SBP decreased significantly from week 4 to week 8, week 8 to week 12, and week 4 to week 12 (p < 0.0001) which were similarly observed in comparison of mean DBP and mean HR during this time.

While comparing independent samples to detect equality of means, baseline mean SBP (167.80 ± 22.88 mmHg, mean ± SD) was higher in the 100 mg metoprolol succinate XL group compared to 50 mg metoprolol succinate XL group (151.60 ± 17.35 mmHg; mean difference = -16.19 ± 3.21 mmHg, mean ± SE, t = -5.04, df = 182, 95% CI = -22.53 to -9.85,p<0.0001). Both the analyses assuming equal variances and unequal variances resulted in significant observations between dosage regimens of metoprolol succinate XL. Baseline DBP of metoprolol succinate XL 100 mg was significantly higher (100.37 ± 11.19 mmHg) than the baseline DBP of metoprolol succinate XL 50 mg (90.24 ± 10.50 mmHg) (mean difference = -10.12 ± 1.81 mmHg, mean ± SE, t = -5.56, df = 182, 95% CI = -13.71 to -6.53, p< 0.0001) (Table 3). However, baseline HR did not differ significantly between the two treatment regimens of metoprolol succinate XL (p> 0.05) while assuming both equal and unequal variances. Apart from that, the mean age of the two treatment regimens did not appear significantly different while considering both equal and unequal variances.

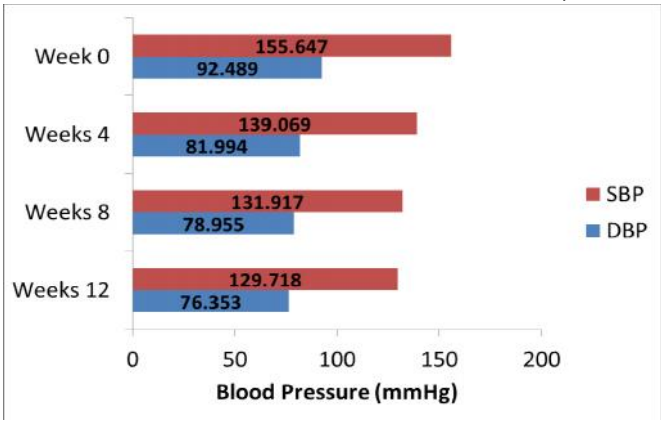

Figure 1: Mean SBP and DBP change from Week 0 to Week 12

*DBP: Diastolic blood pressure; SBP: Systolic blood pressure

Figure 2: Mean HR change from Week 0 to Week 12

*HR: Heart rate

Secondary endpoint:

Distribution of genders did not lead to significant findings in analyses between metoprolol succinate XL 50 mg (47.1% female, 52.9% male) and 100 mg (63% female, 37% male). Distribution of patients with various duration of illness revealed a significant difference between 50 mg and 100 mg metoprolol succinate extended-release groups; patients with 1-10 years of hypertension history were more prevalent (50%) in the 100 mg metoprolol succinate XL group than the 50 mg group (41.3%). Moreover, the Chi-square test revealed a higher proportion of patients with co-morbidities in the 50 mg group (49.6%) than that of the 100 mg group (28.3%) ($p< 0.05$) (Table). While comparing with respect to the global efficacy rating scale, more patients in the 50mg group (84.8%) were associated with excellent efficacy than that in the 100 mg group (63%); however, good efficacy was observed among more patients in the 100 mg group (15.2%) than that of the 50 mg group (8%) ($p \leq 0.05$). The drug demonstrated excellent tolerability among 84.24% of patients and good tolerability among 4.89%; however, 10.33% of patients could not respond to the tolerability rating scale. Further analyses identified 88.4% and 71.7% of patients showing excellent tolerability in the 50 mg and 100mg groups, respectively. On the contrary, more patients (6.5%) in the 100 mg group were associated with good tolerability than in the 50 mg group (4.3%).

Discussion

The study demonstrated that once-daily administration of metoprolol succinate extended-release at 50/100mg dosage significantly reduced mean SBP, mean DBP, and mean HR among hypertensive patients within a 3-month long duration. A considerable proportion of patients completed the study with two dosage regimens, while a higher proportion of patients (75.13%) consumed a lower dosage regimen of metoprolol succinate extended release (50mg). The Independent sample test indicated a significant difference in baseline mean SBP and DBP when comparing 50mg and 100mg dosage regimens, assuming equal and unequal variances. However, baseline mean HR and mean age did not differ significantly between treatment groups among the study population.

Primary efficacy analyses revealed that metoprolol succinate XL 50/100 mg caused more reduction in mean SBP from baseline to 4 weeks (16.57 ± 13.18 mmHg) compared to the 4 weeks to 8 weeks (6.81 ± 8.55 mmHg). Higher mean SBP change in the baseline to 4 weeks group was associated with a larger effect size depicting a Cohen d value of 0.8591, indicating that the decline in mean SBP was practically significant with the study drug among the hypertensive population. However, lower mean SBP change resulted in smaller effect size, as observed in the mean SBP difference between the 4-week to 8-week group (6.81 ± 8.55 mmHg, Cohen d = 0.5030) and between the 8-week to 12-week group (2.19 ± 6.90 mmHg, Cohen d= 0.2191). These observations were retained in the mean DBP difference between the 4-week to 8-week group (3.05 ± 8.02 mmHg, Cohen d = 0.34) and between the 8-week to 12-week group (2.60 ± 6.12 mmHg, Cohen d = 0.34), showing smaller effect size with respect to Cohen d value.

Mean DBP change from baseline to 4-week appeared much higher (10.49 ± 10.50 mmHg) with a larger Cohen d value (0.95) than the mean DBP change between the 4-week and 8-week group. In addition to that, metoprolol succinate extended-release 50/100 mg led to more reduction in mean HR from baseline to 4-week, 8-week, and 12-week consecutively compared to mean HR differences between 4-week and 8-week, 8-week and 12-week, and 4-week and 12-week groups, with evidence of smaller effect size in later groups. A previous study demonstrated a higher ability of metoprolol succinate XL in decreasing SBP, DBP, RPP (rate-pressure product) and HR than amlodipine besylate. Metoprolol succinate extended release appeared more favourable and efficient with respect to reducing BP during early morning, awake, and sleep periods than amlodipine besylate. These findings could be correlated with incidences of myocardial infarction and an ischaemic

stroke reported to occur at a higher frequency during the first 3-4 hours after awakening [2].

Metoprolol succinate XL has been shown to prevent early morning cardiovascular accidents with higher efficacy than other antihypertensive drugs. As a preoperative β-blocker, it has exhibited the potential to minimise the occurrence of non-fatal myocardial infarction, cardiovascular death, and non-fatal cardiac arrest among patients undergoing non-cardiac surgery in a previous randomised, double-blind, and placebo-controlled POISE trial [11]. Its β-antagonism has impacted the sympathetic nervous system by modulating cardiac output, peripheral resistance, and vasodilation, leading to a decrease in oxygen demand to propagate antihypertensive effects. According to primary and secondary preventive studies, β-blockers have presented evidence of cardioprotection in the hypertensive population. They have an established role in showing higher efficacy in the hypertensive diabetic population [7]. The present PMS study findings are consistent with earlier trial results showing reduced blood pressure and heart rate leading to improved overall outcomes [9]. The current study showed a significant lowering of grades of hypertension in just 12 weeks with metoprolol succinate XL. 39.50% of patients went from Grade 1 to Normal, 18% went from Grade 2 to Normal, 61.50% went from High normal to Normal and 45.50% went from isolated systolic hypertension to Normal categories of blood pressure from week 0 to week 12 with metoprolol succinate XL. This reduction in the severity of hypertension directly implies a reduced risk of cardiovascular diseases like stroke, heart failure and myocardial infarction [12]. Inflammation has been linked in the onset of cardiovascular diseases, which shows an association with an elevation in hypertension among individuals. Furthermore, a high level of C-reactive protein (CRP) increases the likelihood of developing cardiovascular complications and is associated with systemic atherosclerosis and low-density lipoprotein cholesterol levels, which have the possibility of raising blood pressure among potential individuals [10,13-17]. Therefore, treatment with metoprolol XL 200mg was beneficial in lowering CRP levels among hypertensive patients contributing to the decline in cases of cardiovascular complications [10]. Apart from that, it appeared safer, tolerable, and more efficient in combination with standard antihypertensive therapies with respect to reducing hypertension among patients.

4. Conclusions

Metoprolol succinate XL 50/100 mg, a selective β-blocker, emerged as a safe antihypertensive medication due to its safety and tolerability profile, associated with a significant reduction in both systolic and diastolic blood pressures and heart rate among patients with hypertension in the African population in a 3-month long course of treatment.

Table 3: SBP change from baseline to end of the treatment

Parameter	Mean	Std. Deviation	Mean difference	Standard deviation for the mean difference	Lower limit for the mean difference at 95% confidence	Upper limit for the mean difference at 95% confidence	t-value	p-value	Effect size (Cohen d)
SBP 0 week	155.647	19.2972	16.578	13.18	14.60	18.56	16.5419	<0.001	0.8591
SBP 4 weeks	139.069	14.3639							
SBP 0 week	155.115	18.3897	23.199	14.92	20.84	25.56	19.4213	<0.001	1.2615
SBP 8 weeks	131.917	10.0360							
SBP 0 week	155.115	18.3897	25.397	15.82	22.90	27.90	20.0543	<0.001	1.3811
SBP 12 weeks	129.718	8.4340							
SBP 4 weeks	138.731	13.5444	6.814	8.55	5.46	8.17	9.9574	<0.001	0.5031
SBP 8 weeks	131.917	10.0360							
SBP 4 weeks	138.731	13.5444	9.013	9.96	7.44	10.59	11.3038	<0.001	0.6654
SBP 12 weeks	129.718	8.4340							

SBP 8 weeks	131.917	10.0360	2.199	6.90	1.11	3.29	3.9780	<0.001	0.2191
SBP 12 weeks	129.718	8.4340							

*SBP: Systolic blood pressure; no. of patients at each visit: week 0= 184, week 12= 156.

Table 4: DBP change from baseline to end of the treatment

Parameter	Mean	Std. Deviation	Mean difference	Standard deviation for the mean difference	Lower limit for the mean difference at 95% confidence	Upper limit for the mean difference at 95% confidence	t-value	p-value	Effect size (Cohen d)
DBP 0 week	92.489	11.0295	10.49	10.51	8.92	12.07	13.18	<0.001	0.95
DBP 4 weeks	81.994	9.7953							
DBP 0 week	92.160	10.8702	13.2051	11.74	11.35	15.06	14.04	<0.001	1.21
DBP 8 weeks	78.955	7.6381							
DBP 0 week	92.160	10.8702	15.8077	12.12	13.89	17.72	16.29	<0.001	1.45
DBP 12 weeks	76.353	7.6477							
DBP 4 weeks	82.006	9.0621	3.0513	8.03	1.78	4.32	4.75	<0.001	0.34
DBP 8 weeks	78.955	7.6381							
DBP 4 weeks	82.006	9.0621	5.6538	8.71	4.28	7.03	8.11	<0.001	0.62
DBP 12 weeks	76.353	7.6477							
DBP 8 weeks	78.955	7.6381	2.6026	6.14	1.63	3.57	5.30	<0.001	0.34
DBP 12 weeks	76.353	7.6477							

DBP: Diastolic blood pressure; no. of patients at each visit: week 0= 184, week 12= 156.

Table 5: HR change from baseline to end of the treatment

	Mean	Std. Deviation	Mean difference	Standard deviation for the mean difference	Lower limit for the mean difference at 95% confidence	Upper limit for the mean difference at 95% confidence	t-value	p-value	Cohen's d (effect size)
HR 0 week	104.572	18.7722	23.05	14.60	20.86	25.24	20.77	<0.001	1.23
HR 4 weeks	81.526	11.7451							
HR 0 week	104.609	19.2627	27.26	15.04	24.88	29.64	22.65	<0.001	1.42
HR 8 weeks	77.346	11.2345							
HR 0 week	104.609	19.2627	29.31	15.07	26.93	31.70	24.30	<0.001	1.52
HR 12 weeks	75.295	10.8611							
HR 4 weeks	81.833	11.6823	4.49	6.42	3.47	5.50	8.73	<0.001	0.38
HR 8 weeks	77.346	11.2345							
HR 4 weeks	81.833	11.6823	6.54	7.45	5.36	7.72	10.97	<0.001	0.56
HR 12 weeks	75.295	10.8611							
HR 8 weeks	77.346	11.2345	2.05	5.34	1.21	2.90	4.80	<0.001	0.18
HR 12 weeks	75.295	10.8611							

HR: Heart rate; no. of patients at each visit: week 0= 184, week 12= 156

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