CLINICAL REVIEW

Application Type	NDA
Application Number(s)	212895
Priority or Standard	S
Submit Date(s)	2/28/19
Received Date(s)	2/28/19
PDUFA Goal Date	12/28/19
Division / Office	DCaRP
Reviewer Name(s)	Maryann Gordon, MD
Review Completion Date	11/1/2019
Established Name	Conjupri
Trade Name	Levamlodipine maleate
Therapeutic Class	3rd generation calcium channel blocker
Applicant	CSPC Ouyi Pharmaceutical Co. Ltd
Formulation(s)	Tablets
Dosing Regimen	Once daily
Indication(s)	Essential hypertension
Intended Population(s)	Adults

Introduction

Changes in racemate or enantiomers of an active ingredient do not require review of information other than bioavailability (BA) or bioequivalence (BE) studies.[1]. The approval of levoamlodipine maleate in this 505(b)(2) new drug application (NDA) for the treatment of hypertension is mainly based on BE data from the pivotal BA/BE study, given that the anti-hypertensive efficacy of the reference listed drug (RLD) (NORVASC® by Pfizer) as a calcium channel blocker has been well established. Despite this, the sponsor conducted three clinical trials that evaluated safety and efficacy of levoamlodipine as an antihypertensive agent. These studies were reviewed by the division in a cursory manner without statistical analyses. Therefore, this review relies solely on the study reports submitted by the sponsor. The results of each of the studies are attached to this review.

Efficacy and safety summary

The efficacy data obtained from the three clinical studies conducted by the sponsor with levoamlodipine maleate tablet have generally shown that levoamlodipine maleate tablets at 2.5 mg/day produced similar antihypertensive efficacy compared to NORVASC® at 5 mg/day in hypertensive patients.

The safety findings from the three clinical studies demonstrated that the overall safety profile of levoamlodipine maleate appears to be similar to NORVASC®.

[1] *FDA Guidance for Industry: Applications Covered by Section 505(b)(2)*

Table 4. Supportive Efficacy Data from the CSPC-Sponsored Studies

Study Name	Title	Study Period	Design	Efficacy Conclusion
Efficacy and Safety Study in China	A Multicenter, Randomized, Double-blind, Parallel, Active Controlled Phase IV Efficacy and Safety Study of Levoamlodipine Maleate for Treatment of Mild-Moderate Primary Hypertension (Study 022071021)	Nov 2007-Dec 2008	204 patients (101 in levoamlodipine group and 103 in NORVASC® group)	Compared with NORVASC®, levoamlodipine demonstrated similar efficacy for the treatment of mild to moderate primary hypertension.
Ambulatory BP and LVH Study	Multicenter and random clinical study on ambulatory blood pressure and left ventricle mass effect of hypertensive patients by the treatment of levoamlodipine maleate	Jan 2009-Jul 2010	196 patients in the 2 groups, average age was 59 years old.	The treatment effect for levoamlodipine was similar to amlodipine in hypertensive patients with cardiovascular risk factors.
LEADER Study	Levoamlodipine Maleate or Amlodipine Besylate for Treatment of Hypertension: A Comparative Effectiveness Study (LEADER)	Feb 2013 - Dec 2016	In real-world setting, 10031 outpatients at 110 centers in China; were treated with 2.5 mg/d levoamlodipine or 5 mg/d amlodipine; followed for 2 years for BP and MACCE	The antihypertensive effectiveness and occurrence of MACCE with levoamlodipine maleate were similar compared with amlodipine.

BP = blood pressure; CV = cardiovascular; LVH = left ventricular hypertrophy; MACCE = major cardiovascular and cerebrovascular events

The Efficacy and Safety Study was conducted in 204 patients (101 patients in the levoamlodipine group and 103 patients in NORVASC® group) with an 8-week double-blinded treatment period. The absolute reductions on DBP at the end of Week 10 from baseline at week 2 (primary efficacy endpoint) were 14.84±7.59 mmHg in the levoamlodipine group and 15.02±6.36 mmHg in the NORVASC® group, respectively. The absolute reductions on SBP at the end of Week 10 from baseline at week 2 (secondary efficacy endpoint) were 17.32±11.28 mmHg in the levoamlodipine group and 19.71±11.73 mmHg in the NORVASC® group, respectively.

The Ambulatory BP and LVH Study was conducted in 196 patients with essential hypertension associated with one or more cardiovascular risk factors. After a 2-week washout period, eligible patients were randomized at a ratio of 1:1 to receive treatment with either 2.5 mg/day levoamlodipine maleate (Group A) or 2.5 mg/day of amlodipine besylate plus 0.5

tablet/day of amiloride plus 40 mg/day of telmisartan (Group B), for up to 18 months. Efficacy endpoints included 24-hour ambulatory blood pressure at 8 weeks. The results demonstrated significant reductions in clinic and 24-hour ambulatory blood pressure in both groups.

The LEADER Study was conducted in 10,031 patients enrolled at 110 centers in 21 cities in China. Patients were treated with either 2.5 mg/day levoamlodipine (N=5,018) or 5 mg/day amlodipine (N=5,013) for up to 2 years. Follow-up visits were scheduled at 1, 2, 3, 6, 12, 18, and 24 months after the start of treatment. The main objectives were to evaluate the effects of long-term use of either levoamlodipine or amlodipine on blood pressure and cardiovascular events. The secondary objectives were to evaluate adverse reactions and cost effectiveness. At the end of study, blood pressure had decreased in a similar manner for both drugs: SBP was 129.92±7.01 and 131.26±7.22 mmHg, and DBP was 77.46±5.74 and 77.86±6.21 mmHg in the levoamlodipine and amlodipine groups, respectively.

Study name
Efficacy and Safety Study in China

Title
A Multicenter, Randomized, Double-blind, Parallel, Active Controlled Phase IV Efficacy and Safety Study of Levoamlodipine Maleate for Treatment of Mild-Moderate Primary Hypertension

Study objective
The study is designed to evaluate the efficacy and safety of levoamlodipine maleate (hereafter referred to as (b) (4)) for treatment of mild-moderate primary hypertension.

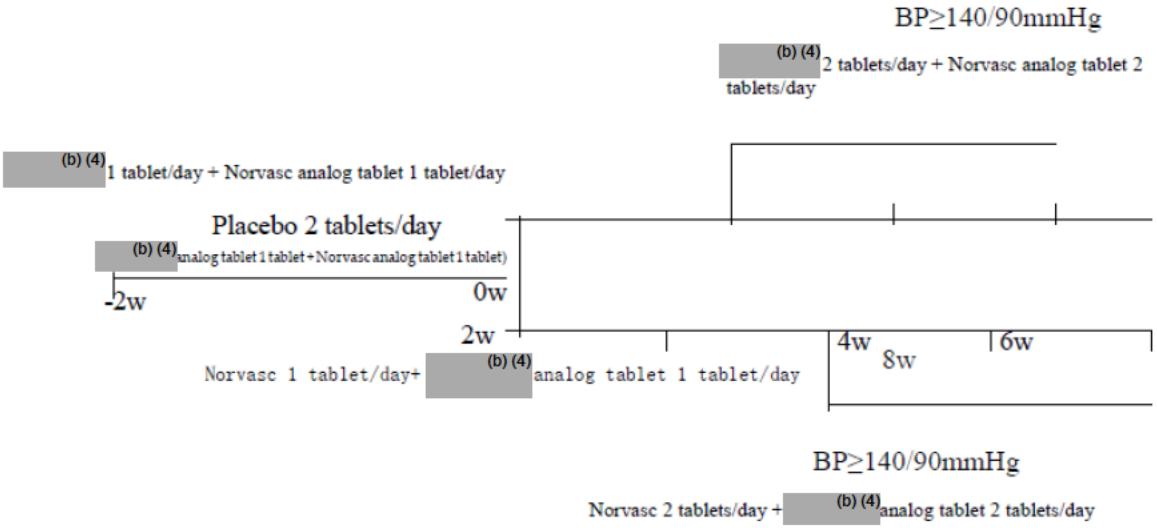
Study design
This study is a multicenter, randomized, double-blind, double-dummy, parallel and controlled clinical study.

Study cycle
• 2 weeks of placebo washout period (screening phase).

• The patients whose DBP was 95 mmHg or more were randomized to either levoamlodipine maleate at 2.5 mg/day as the initial dose or amlodipine besylate at 5mg/day as the initial dose. Patients who reached the target blood pressure (sitting blood pressure＜140/90 mmHg) after 4 weeks continued the same study drug at the same dose until the end of the study.

• Patients whose blood pressure didn't reach the target at the end of 4 weeks received doubled doses of 5 mg/day of levoamlodipine maleate or 10mg/day of amlodipine and continued in the study for another 4 weeks.

The study scheme is shown below.



Inclusion criteria

(1) Voluntarily participated and signed the informed consent;
(2) Male or female patients between 18 and 70 years of age;
(3) Mild-moderate primary hypertension, 95 mmHg ≤ DBP ＜110 mmHg and SBP ＜180 mmHg;
(4) Not associated with serious heart, brain, kidney and other organ damage;
(5) Body mass index (BMI)≤30 (kg/m2).

Exclusion Criteria

(1) Hypertension combined with the following conditions within the past 5 months: history of cerebrovascular incidents, myocardial infarction or heart failure, aneurysm or aortic dissection; definite angina, II degree and above atrioventricular block, sick sinus syndrome, and malignant or potential malignant arrhythmias;
(2) Secondary hypertension;
(3) Seriously abnormal cardio-pulmonary function;
(4) Unstable glycemic control of diabetes, fasting blood glucose ＞ 11.1 mmol/l, or with complications (nephropathy, peripheral neuropathy);
(5) Patients with gastrointestinal lesions or whose drug absorption may be affected after gastrointestinal surgery;
(6) Untreated thyroid disease;
(7) Electrolyte imbalance, including serum potassium＜ 3.5 mmol/L or ＞ 5.5 mmol/L; Impaired liver and kidney function: AST and/or ALT exceeding one times or more than the upper limit of normal;
(8) Creatinine exceeding the upper limit of normal (133 μmol/L);
(9) Autoimmune diseases or any other serious physical illness, which may affect the patient's ability to successfully participate in the study;
(10) Pregnant or lactating women;
(11) Mental illness, without self-control;
(12) Participated in any other clinical studies within the last 2 months;
(13) Having any allergy or contraindications to the study drugs;
(14) Other conditions that the study investigators believed should be excluded.

Efficacy Assessment

Primary Efficacy Measures

Efficacy was assessed by the absolute value change of DBP after the double-blind treatment for 4 weeks and 8 weeks from the DBP at the beginning of the double-blind treatment (0 week). Ambulatory blood pressure monitoring (ABPM) was also assessed during double-blind treatment period.

Results

There were 204 patients enrolled in this study. The study drug group had 101 patients with 95 patients completing the study. The control group had 103 patients with 95 patients completing the study.

The safety analysis set included patients who had received at least one dose of the study drug and had at least one safety evaluation.

Table 13-1 Study Population Statistics by Study Center

	Norvasc group N (%)	(b) (4) group N (%)	Statistics
Total			
Randomized	103	101	
Completed	95(92.23)	95(94.06)	0.2661
withdrawn	8(7.77)	6(5.94)	
Efficacy analysis set	99(96.12)	97(96.04)	
Safety analysis set	103(100)	101(100)	

Demographics

Both groups had 54% males, mean age was about 52 years (with the youngest being 27 years and the oldest 78 years). Baseline mean blood pressures are shown below.

Table 13-7 Baseline Blood Pressure

Systolic blood pressure (mmHg)	Norvasc group	(b) (4) group	S
N (Missing)	99(0)	97(0)	
Mean ± SD	149.56 ± 10.29	148.08 ± 12.40	
Median	149.00	148.00	
Min~Max	123.00-173.00	120.00-177.00	
LCLM-ULCLM	147.50-151.61	145.58-150.58	
Diastolic blood pressure (mmHg)			
N (Missing)	99(0)	97(0)	
Mean ± SD	98.61 ± 4.02	97.79 ± 3.02	
Median	97.00	97.00	
Min~Max	92.00-114.00	91.00-108.00	

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Baseline blood pressure in the two treatment groups was similar.

BP effects

The absolute reduction in DBP at week 4 from baseline is shown in the table below.

Table 14-3 Reduction of Average DBP for 4 Weeks (mmHg)

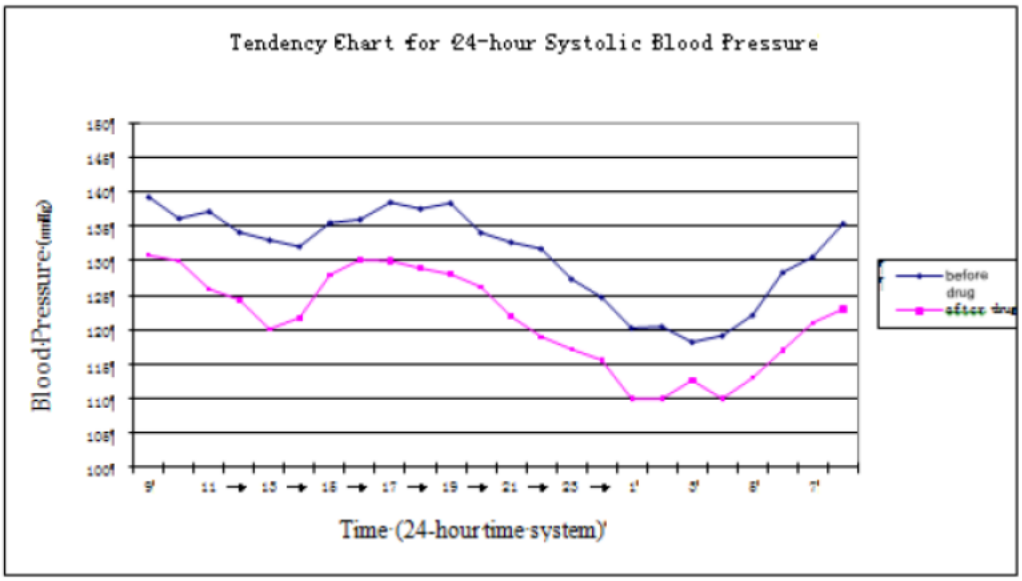
	Norvasc	(b) (4)	Statistic
N(Missing)	99(0)	97(0)	Pooled
Mean ± SD	11.65 ± 7.52	10.35 ± 8.72	
Median	10.00	10.00	
Min-Max	-4.00-33.00	-12.00-33.00	
95%CI(L~H)	10.15-13.15	8.59-12.11	

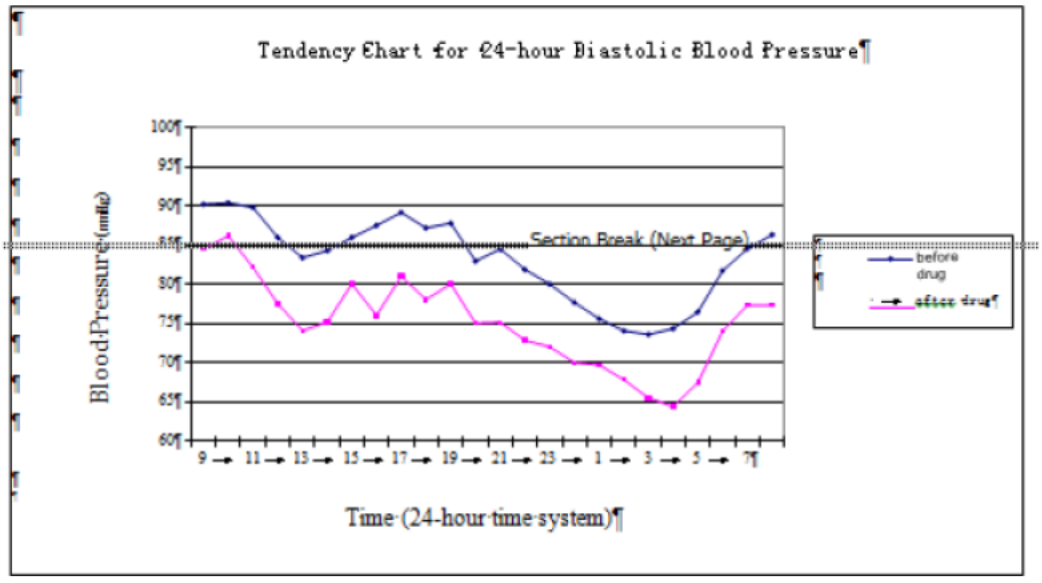
The mean reduction in DBP was similar for the two treatment groups.

Ambulatory BP measurements

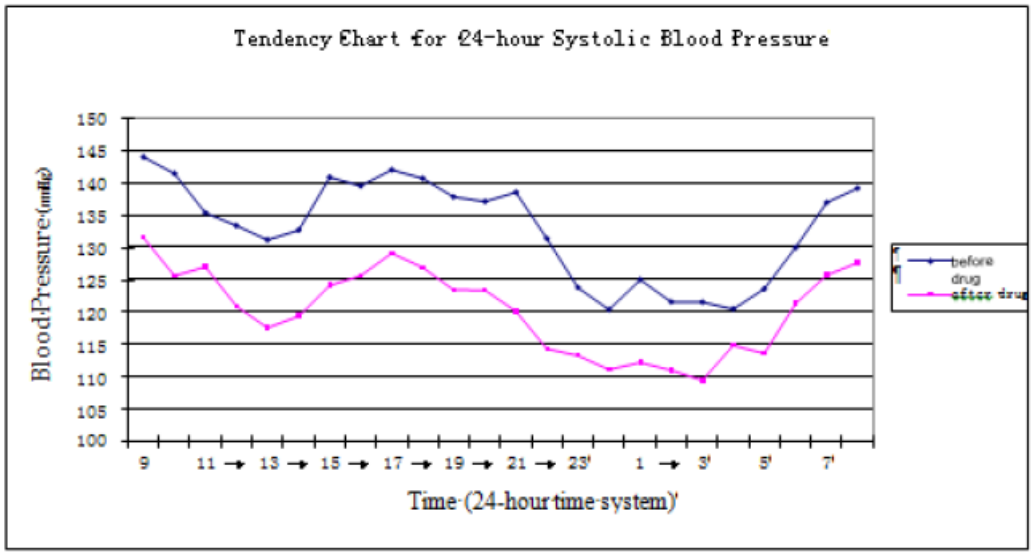
The figures below show the 24-hour BP measurements before study drug (visit 2) and at week 8 (visit 6).

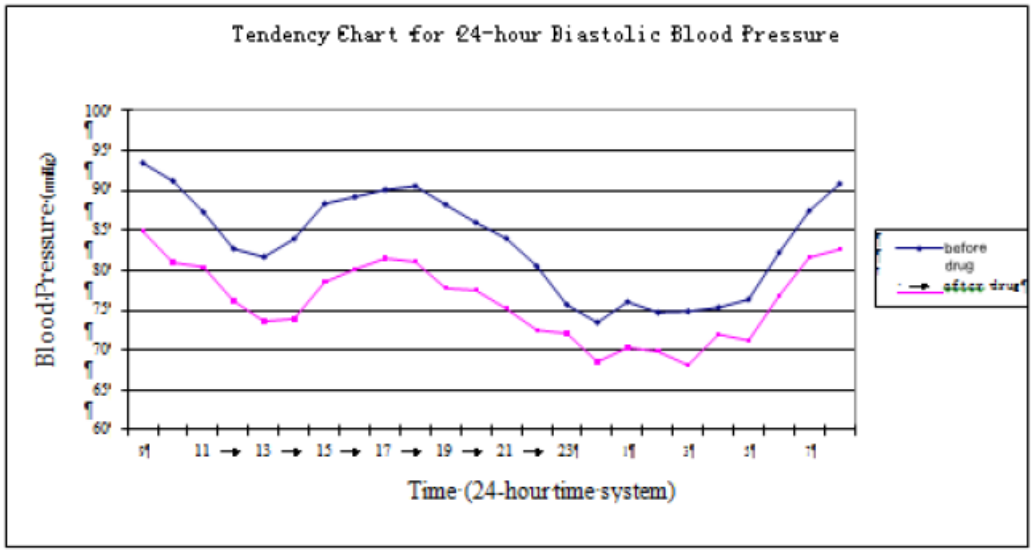
Tendency chart for 24-hour blood pressure of [redacted] (b) (4) group (37 cases) are shown below.





Tendency chart for 24-hour blood pressure of Norvasc group (32 cases) are shown belo





The changes in 24-hour BP measurements at week 8 are similar for both drugs.

Safety

Adverse event occurrence rates for the Norvasc and (b) (4) groups were 15% and 11%, respectively, and the rates of drug-related adverse events or adverse drug reactions (ADR) were 7% and 2%, respectively. AE and adverse reaction rates for the two groups were similar.

Table 15-7 Adverse Events/Adverse Drug Reactions Summary

	Norvasc (103 patients)			[redacted] (b) (4) (101 patients)		
	# Events	# Patients	rate	# Events	# Patients	rate
All adverse events	15	15	14.85%	13	11	11.11%
Adverse events leading to discontinuation	0	0	0	0	0	0
Adverse reactions*	7	7	6.93%	2	2	2.02%
Adverse reactions leading to discontinuation	0	0	0	0	0	0

Individual reported adverse events are shown in the table below.

Table 15-9 Preferred Terms and Frequency of Adverse Reaction

Name of adverse reaction	Norvasc (103 patients)		[redacted] (b) (4) (101 patients)	
	Number	Frequency (%)	Number	Frequency (%)
Both lower extremities/ankle edema/dropsy edema peripheral	3	2.91%	0	0
Liver function test abnormal	1	0.97%	0	0
Abdominal discomfort	1	0.97%	0	0
Dizziness	1	0.97%	2	1.98%
Palpitation	1	0.97%	0	0

Reported adverse events are similar between the two treatment groups.

Study name
Ambulatory BP and LVH study

Title
Multicenter and Random Clinical Study on Ambulatory Blood Pressure and Left Ventricle Mass Effect of Hypertensive Patients by the Treatment of Levoamlodipine Maleate (Ambulatory BP and LVH Study)

The study was conducted exclusively in China.

Primary Objectives
To evaluate the effect of levoamlodipine maleate on ambulatory blood pressure monitoring (ABPM) and left ventricular hypertrophy (LVH).

The study was conducted with amlodipine besylate as the active control in a total of 196 patients with essential hypertension defined as sitting blood pressure 140-179 or/and 90-109 mmHg) after two-week washout period.

After the 2-week washout period, qualified patients were randomized 1:1 to the levoamlodipine maleate group (Group A) or the amlodipine besylate group (Group B). The initial dose was

Doses
Group A: 2.5 mg/day levoamlodipine maleate

Group B: 2.5 mg/day of amlodipine besylate+0.5 tablet/day of amiloride compound+40 mg/day of telmisartan for Group B.

After 2, 4, and 8 weeks of treatment, study drug doses were increased based on blood pressure response. Target blood pressure response was <140/90 mmHg.

Efficacy endpoints
Included clinical blood pressure recordings, 24-hour ABPM at 8 weeks, and echocardiography. The treatment period was18 months.

ABPM Spacelabs90217 type ambulatory blood pressure monitoring of the United States was used for ABPM. The subjects installed the ABPM measurement device between 8-10AM with the cuff tied to the left upper limb and set up to automatically inflate and measure the blood pressure once every 20 minutes during the day (06:00-22:00) and every 30 minutes at night (22:00-06:00). The measurement time was not less than 24 hours with the effective measurement time ≥ 85%. The statistical analysis parameters were as follows: 24-hour average systolic blood pressure (24hSBP), 24-hour average diastolic blood pressure (24hDBP), daytime average systolic blood pressure (dSBP), daytime average diastolic blood pressure (dDBP), nighttime average systolic blood pressure (nSBP) and nighttime average diastolic pressure (nDBP). The calculation formula of variable coefficient used for representing the blood pressure variation was standard deviation/mean. Ambulatory blood pressure measurements were processed uniformly

by the professional and technical personnel in the hypertension office at [redacted] (b) (4)

Echocardiography Measurement HPsonos-5500 and HPsonos-7500 type of ultrasonic diagnostic apparatus was used with 2~4MHz of transducer frequency. The subject underwent M-mode (50 mm/s) and 2-dimensional imaging using the long-axis view. The measurements were online, and the images were saved. Three cardiac cycles were recorded, taking the average value. Left ventricular end diastolic diameter (LVDD), left ventricular posterior wall diastolic thickness (LVPWT) and
interventricular septal thickness (IVST) were measured according to the recommendations of the American Society of Echocardiography. Left ventricular mass (LVM) and left ventricular mass index (LVMI) were calculated by the Devereux correction formula. Body surface area was calculated using the Stevenson formula. The enlargement standard for LVMI was male＞ 115g/m^2 and female＞95g/m^2.
① Left Ventricular Mass=0.80[1.04×(LVDD+IVST+LVPWT)3－LVDD3]+0.6
② Left Ventricular Mass Index= LVM/BSA (Body surface area)
③ BSA＝0.0061×Height(cm)+0.0128×Weight(kg)－0.1529
④E/A ratio= maximum flow velocity of mitral valve for early diastole (E)/ maximum flow velocity for later diastole (A).

Echocardiogramswere processed uniformly by the echocardiographic expert and technical personnel from [redacted] (b) (4)

Results
There was a total of 196 subjects randomized (Group A 103 and Group B 93).

Clinical Blood Pressure
The figure below shows changes in blood pressure in the two groups during the treatment period.

Table 3 Comparison of Clinic Blood Pressure Change before and after Treatment (x±s, mmHg)

	In random	One month	Two months	Three months	Six months	Twelve Months	Eighteen months
A group	154.2/92.8	133.6/82.3	132.2/80.9	130.7/85.1	131.1/80.9	129.6/78.3	129.4/80.1
B group	153.4/92.1	130.0/80.2	128.8/79.0	128.2/78.6	132.3/80.5	128.3/78.7	131.8/80.5

At randomization, the blood pressures were 154/93 mmHg for Group A and 153/92 mmHg for Group B. The changes in blood pressure of the two groups were similar throughout the study.

ABPM

There were 96 and 87 patients in A group and B group who finished the ABPM examination, respectively, at baseline and at week 8. The parameters evaluated included 24-hour systolic

blood pressure (24hSBP), 24-hour diastolic blood pressure (24hDBP), daytime average systolic blood pressure (dSBP), daytime average diastolic blood pressure (dDBP), nighttime average systolic blood pressure (nSBP) and nighttime average diastolic pressure (nDBP). The results at baseline and week 8 are shown in the table below.

Table 4 Comparison of Ambulatory Blood Pressure

Group	24hSBP		24hDBP		dSBP		dDBP		nSBP		nDBP	
	Baseline	8 weeks	Baseline	8 weeks	Baseline	8 weeks	Baseline	8 weeks	Baseline	8 weeks	Baseline	8 weeks
A group	133.34	123.30	83.45	78.02	134.85	125.94	84.73	80.15	128.39	115.63	79.28	71.95
B group	135.29	121.79	81.61	78.45	138.11	124.92 *	83.55	80.25	127.97	113.16	76.47	72.70

These results show that treatment with levoamlodipine maleate in this study reduced 24-hour ambulatory blood pressure that was similar to the results for amlodipine besylate.

Echocardiography

There were 93 and 87 selected patients in A group and B group who completed the echocardiography examination, respectively. The table below shows left ventricular mass (LVM) and left ventricular mass index (LVMI) at baseline and after 18 months of antihypertensive treatment.

Table 5 LVM and LVMI for Echocardiography before and after Treatment

Group	Baseline		18 months after treatment	
	LVM (g)	LVMI (g/m^2)	LVM (g)	LVMI (g/m^2)
A group	164.28 ±43.88	92.03 ±20.83	159.90 ±36.62	89.36 ±16.32
B group	163.51 ±48.08	91.20 ±23.11	159.98 ±42.76	89.39 ±19.25

These results show that treatment with either levoamlodipine maleate or amlodipine besylate reduced LVM and LVMI measurements in a similar manner.

Safety

No safety results were reported in the study report.

In conclusion, compared with amlodipine besylate, levoamlodipine maleate demonstrated similar efficacy for the treatment of mild to moderate primary hypertension. Safety was not evaluated.

Study name

LEADER study

Study title

Levoamlodipine Maleate or Amlodipine Besylate for Treatment of Hypertension: A Comparative Effectiveness Study

Introduction

This was a prospective multicenter real-world study of outpatients with primary hypertension treated with levoamlodipine maleate or benzenesulfonate amlodipine exclusively in China.

The baseline data included the general clinical characteristics, previous medical histories, combined drug therapy (especially the antihypertensive drugs), and physical examination results. Once included, bilateral blood pressures were measured and the arm with the higher SBP was selected for the remaining of the study.

All patients were followed up for 2 years after enrollment, at 1, 2, 3, 6, 12, 18 and 24 months. Physical examination, adverse events, and outcomes were assessed.

The main study outcome was to assess the effects of levoamlodipine maleate and benzenesulfonate amlodipine on the occurrence of MACCE in patients with primary hypertension. The composite outcome included: 1) death, including fatal cerebral stroke, fatal myocardial infarction, sudden death, any death caused by cardiovascular diseases, any death caused by non-cardiovascular events, and any death caused by any other reasons; 2) non-fatal myocardial infarction, unstable angina pectoris, and coronary arterial revascularization therapy; 3) ischemic cerebral stroke, hemorrhagic cerebral stroke, and transient cerebral ischemic attack; 4) aortic dissecting aneurysm, interventional therapy for peripheral artery, or other surgeries for artery; 5) hospitalization for heart failure; and 6) newly developed atrial fibrillation.

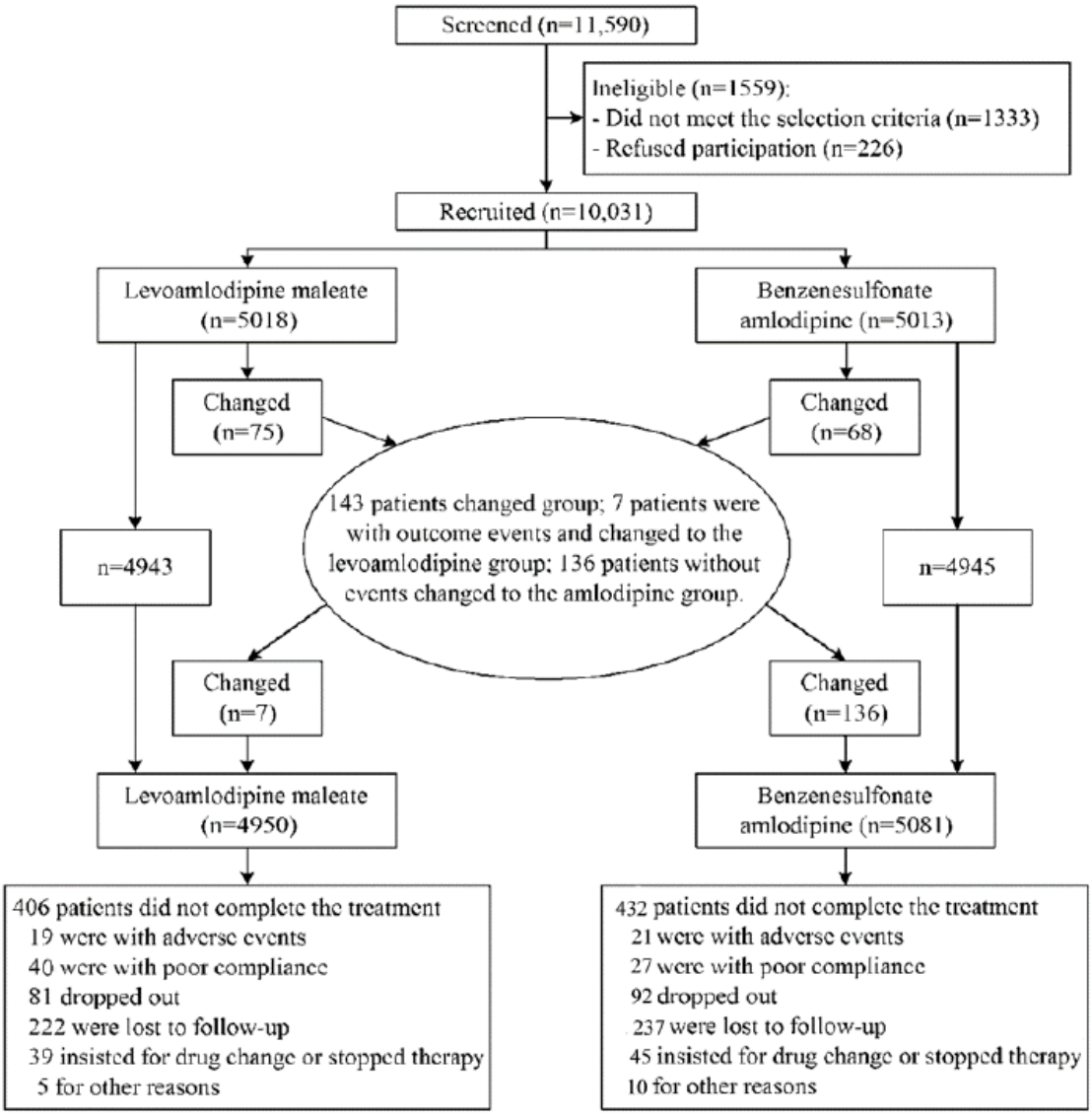
The secondary outcomes were safety, hypertensive effect, and pharmacoeconomics.

The drug-related AEs such as edema of the lower extremities, facial flushing, dizziness, headache, fatigue, palpitation, abdominal pain, gingival pain and swelling, nausea, somnolence, and other adverse reactions were recorded.

Results

The final number of study patients was 10,031: 5018 were in the levoamlodipine maleate group and 5013 were in the benzenesulfonate amlodipine group. 143 patients were switched to the other group by their physician: 75 in the levoamlodipine maleate group and 68 in the benzenesulfonate amlodipine group. In the final analysis, 4950 patients were in the levoamlodipine maleate group and 5081 were in the benzenesulfonate amlodipine group.

The patient flow chart for the 2-year study is shown below.



Dropouts were 8% for each treatment group.

Half the patient population was male, mean age was 64 years. The BMI, SBP, DBP, heart rate, and percentage of smoking were slightly higher in the levoamlodipine maleate group than in the benzenesulfonate amlodipine group. More patients in the levoamlodipine maleate group were concurrently using ACEI/ARB than in the benzenesulfonate amlodipine group while the combined use of other drugs was not significantly different between the two groups. The frequency of statin use was lower in the levoamlodipine maleate group than in the benzenesulfonate amlodipine group. After matching, 3946 patients were selected in each group.

Blood pressure at the end of study and use of antihypertensive drugs

At the end of study (after completing the 24-month follow-up for each patient), the SBP was 129.92±7.01 and 131.26±7.22 mmHg (adjusted $P<0.001$), while the DBP was 77.46±5.74 and

77.86±6.21 mmHg in the levoamlodipine maleate and benzenesulfonate amlodipine groups, respectively.

Baseline BP control rate was slightly higher in the levoamlodipine maleate group than benzenesulfonate amlodipine group, while the BP control rate at the end of 24-month follow-up was slightly higher in the benzenesulfonate amlodipine group (94%) than levoamlodipine maleate group (91%).

The reported MACCE percentage was 5% for both treatment groups.

Table 2. Survival analysis of the composite outcome

Event	levoamlodipine maleate	benzenesulfonate amlodipine
MACCE[1]	226 (4.6%)	256 (5.0%)
Death	19 (0.4%)	20 (0.4%)
Coronary heart disease[2]	72 (1.5%)	95 (1.9%)
Stroke[3]	119 (2.4%)	125 (2.5%)
Aortic dissection/ interventional treatment for peripheral artery/ surgeries for arterial diseases	4 (0.1%)	3 (0.1%)
Hospitalization for heart failure	12 (0.2%)	16 (0.3%)
Newly developed atrial fibrillation	6 (0.1%)	14 (0.3%)

[1]Composite outcome events include death, coronary heart diseases, stroke, aortic dissection, interventional treatment and surgery for peripheral arteries, and re-hospitalization for heart failure.

[2]Coronary heart diseases include angina pectoris, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass surgery.

[3]Stroke include ischemic cerebral stroke, hemorrhage cerebral stroke, TIA, and other cerebral vascular diseases.

Adverse reactions

The reports of adverse events were significantly lower in the levoamlodipine maleate group compared to benzenesulfonate amlodipine group (5% vs. 7%). Among the reported adverse reactions, the occurrence of lower extremity edema was lower in the levoamlodipine maleate group than in the benzenesulfonate amlodipine group (1% vs. 3%). The other adverse reactions such as facial flushing, gingival pain and swelling, headache, and dizziness were similar between the two groups.

Table 3. Comparison of the adverse reactions between the two groups

	Full dataset		
	Levoamlodipine maleate	Benzenesulfonate amlodipine	Total
Lower extremity edema	41 (0.8%)	130 (2.6%)	171 (1.7%)
Facial flushing	26 (0.5%)	33 (0.6%)	59 (0.6%)
Gingival pain and swelling	14 (0.3%)	16 (0.3%)	30 (0.3%)
Dizziness	98 (2.0%)	99 (1.9%)	197 (2.0%)
Headache	31 (0.6%)	41 (0.8%)	72 (0.7%)
Fatigue	19 (0.4%)	16 (0.3%)	35 (0.3%)
Abdominal pain and nausea	5 (0.1%)	6 (0.1%)	11 (0.1%)
Palpitations	19 (0.4%)	22 (0.4%)	41 (0.4%)
Somnolence	4 (0.1%)	8 (0.2%)	12 (0.1%)
Other	29 (0.6%)	34 (0.7%)	63 (0.6%)

In the study, there was very little difference in patient outcome between the two treatment groups.

Title

Multicenter, Randomized, Double-blind, Parallel, Active Controlled Phase IV Efficacy and Safety Study of Levoamlodipine Maleate for Treatment of Mild-Moderate Primary Hypertension

Study objective

The study is designed to evaluate the efficacy and safety of levoamlodipine maleate (hereafter referred to as (b) (4) for treatment of mild-moderate primary hypertension.

Study design

This study is a multicenter, randomized, double-blind, double-dummy, parallel and controlled clinical study.

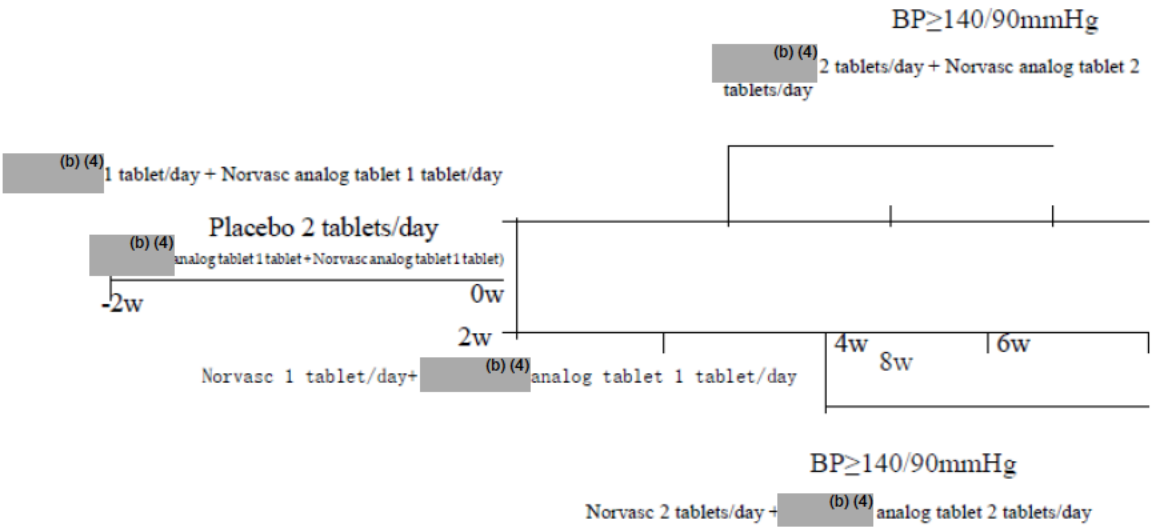
Study cycle

• 2 weeks of placebo washout period (screening phase).

• The patients whose DBP was 95 mmHg or more were randomized to either levoamlodipine maleate at 2.5 mg/day as the initial dose or amlodipine besylate at 5mg/day as the initial dose. Patients who reached the target blood pressure (sitting blood pressure＜140/90 mmHg) after 4 weeks continued the same study drug at the same dose until the end of the study.

• Patients whose blood pressure didn't reach the target at the end of 4 weeks received doubled doses of 5 mg/day of levoamlodipine maleate or 10mg/day of amlodipine and continued in the study for another 4 weeks.

The study scheme is shown below.



Inclusion criteria

(1) Voluntarily participated and signed the informed consent;
(2) Male or female patients between 18 and 70 years of age;

(3) Mild-moderate primary hypertension, 95 mmHg ≤ DBP ＜ 110 mmHg and SBP ＜180 mmHg
(4) Not associated with serious heart, brain, kidney and other organ damage;
(5) Body mass index (BMI) ≤ 30 (kg/m2).

Exclusion Criteria
(1) Hypertension combined with the following conditions within the past 5 months: history of cerebrovascular incidents, myocardial infarction or heart failure, aneurysm or aortic dissection; definite angina, II degree and above atrioventricular block, sick sinus syndrome, and malignant or potential malignant arrhythmias;
(2) Secondary hypertension;
(3) Seriously abnormal cardio-pulmonary function;
(4) Unstable glycemic control of diabetes, fasting blood glucose ＞ 11.1 mmol/l, or with complications (nephropathy, peripheral neuropathy);
(5) Patients with gastrointestinal lesions or whose drug absorption may be affected after gastrointestinal surgery;
(6) Untreated thyroid disease;
(7) Electrolyte imbalance, including serum potassium ＜ 3.5 mmol/L or ＞ 5.5 mmol/L; Impaired liver and kidney function: AST and/or ALT exceeding one times or more than the upper limit of normal;
(8) Creatinine exceeding the upper limit of normal (133 μmol/L);
(9) Autoimmune diseases or any other serious physical illness, which may affect the patient's ability to successfully participate in the study;
(10) Pregnant or lactating women;
(11) Mental illness, without self-control;
(12) Participated in any other clinical studies within the last 2 months;
(13) Having any allergy or contraindications to the study drugs;
(14) Other conditions that the study investigators believed should be excluded.

Efficacy Assessment
Primary Efficacy Measures
Efficacy was assessed by the absolute value change of DBP after the double-blind treatment for 4 weeks and 8 weeks from the DBP at the beginning of the double-blind treatment (0 week). Ambulatory blood pressure monitoring (ABPM) was also assessed during double-blind treatment period.

Results
There were 204 patients enrolled in this study. The study drug group had 101 patients with 95 patients completing the study. The control group had 103 patients with 95 patients completing the study.

The safety analysis set included patients who had received at least one dose of the study drugs and had at least one safety evaluation.

Table 13-1 Study Population Statistics by Study Center

	Norvasc group N (%)	(b) (4) group N (%)	Statistics
Total			
Randomized	103	101	
Completed	95(92.23)	95(94.06)	0.2661
withdrawn	8(7.77)	6(5.94)	
Efficacy analysis set	99(96.12)	97(96.04)	
Safety analysis set	103(100)	101(100)	

Demographics

Both groups had 54% males, mean age was about 52 years (with the youngest being 27 years and the oldest 78 years). Baseline mean blood pressures are shown below.

Table 13-7 Baseline Blood Pressure

Systolic blood pressure (mmHg)	Norvasc group	(b) (4) group	S
N (Missing)	99(0)	97(0)	
Mean ± SD	149.56 ± 10.29	148.08 ± 12.40	
Median	149.00	148.00	
Min~Max	123.00-173.00	120.00-177.00	
LCLM-ULCLM	147.50-151.61	145.58-150.58	
Diastolic blood pressure (mmHg)			
N (Missing)	99(0)	97(0)	
Mean ± SD	98.61 ± 4.02	97.79 ± 3.02	
Median	97.00	97.00	
Min~Max	92.00-114.00	91.00-108.00	

Baseline blood pressure in the two treatment groups were similar.

BP effects

The absolute reduction in DBP at week 4 from baseline is shown in the table below.

Table 14-3 Reduction of Average DBP for 4 Weeks (mmHg)

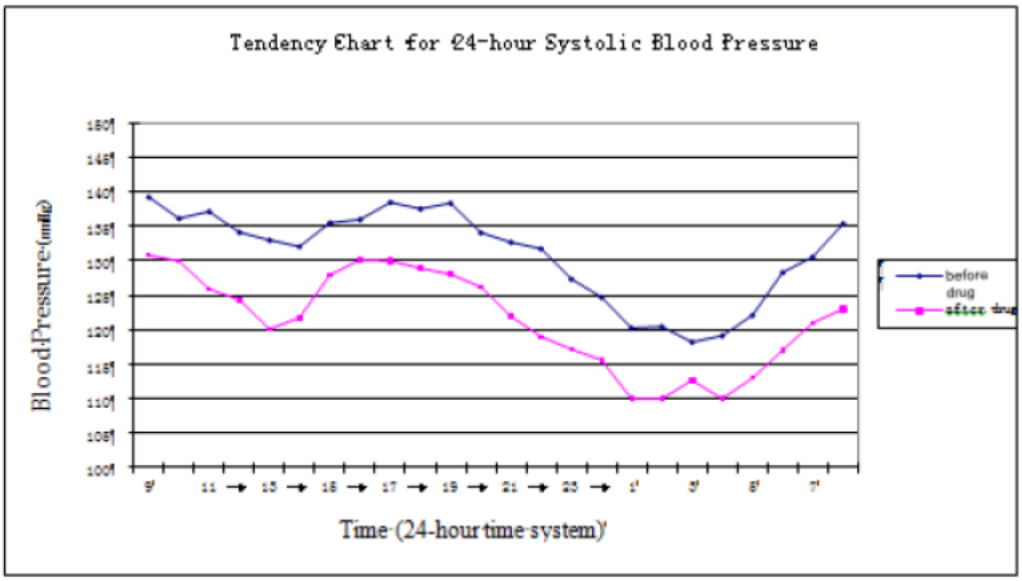
	Norvasc	(b) (4)	Statistic
N(Missing)	99(0)	97(0)	Pooled
Mean ± SD	11.65 ± 7.52	10.35 ± 8.72	
Median	10.00	10.00	
Min-Max	-4.00-33.00	-12.00-33.00	
95%CI(L~H)	10.15-13.15	8.59-12.11	

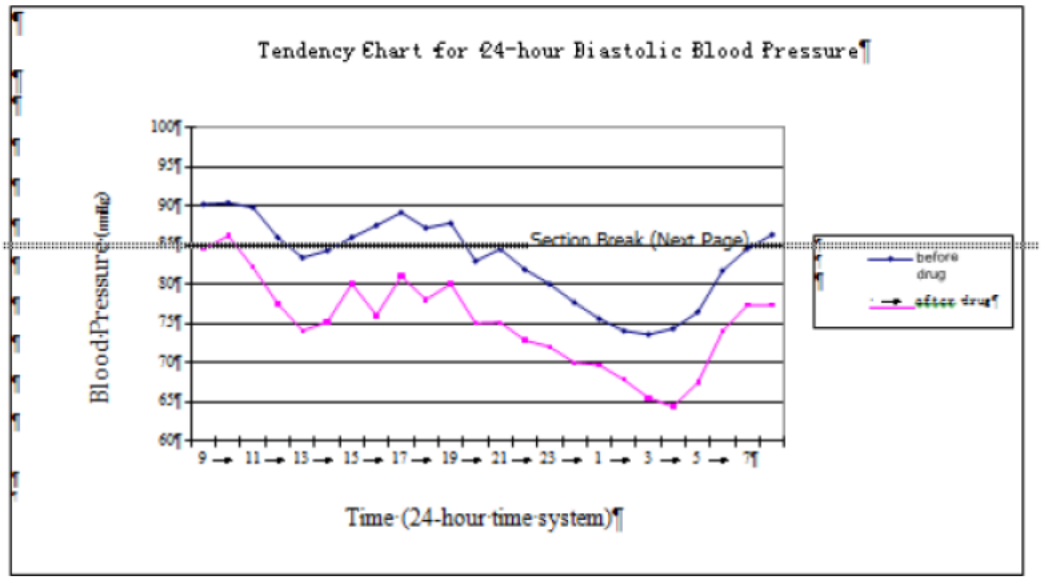
The mean reduction in DBP was similar for the two treatment groups.

Ambulatory BP measurements

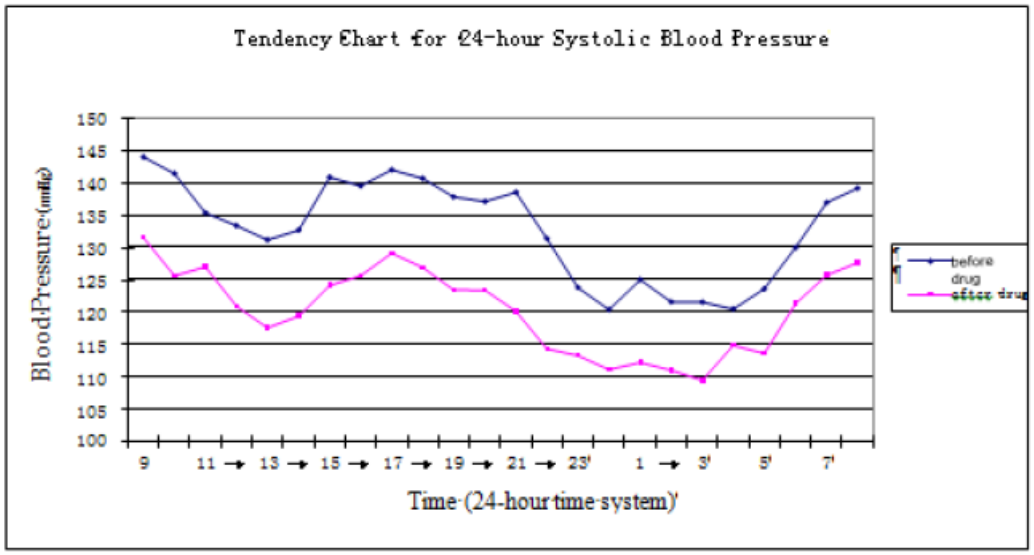
The figures below show the 24-hour BP measurements before study drug (visit 2) and at week 8 (visit 6).

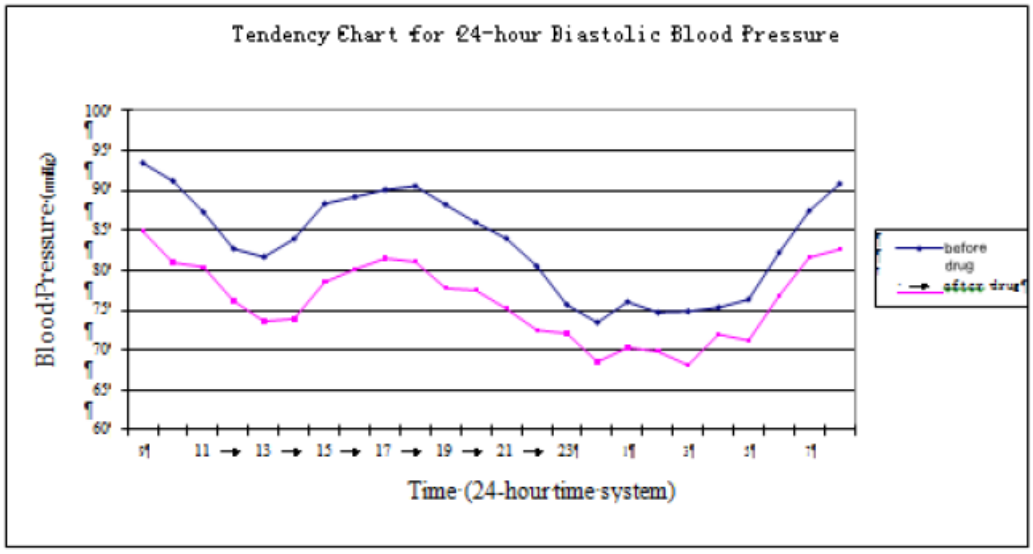
Tendency chart for 24-hour blood pressure of (b) (4) group (37 cases) are shown below.





Tendency chart for 24-hour blood pressure of Norvasc group (32 cases) are shown belo





The changes in 24-hour BP measurements at week 8 are similar for both drugs.

Safety

Adverse event occurrence rates for the Norvasc and (b) (4) groups were 15% and 11%, respectively, and the rates of drug-related adverse events or ADRs were 7% and 2%, respectively. AEs and adverse reaction rates for the two groups were similar.

Table 15-7 Adverse Events/Adverse Drug Reactions Summary

	Norvasc (103 patients)			[redacted] (b) (4) (101 patients)		
	# Events	# Patients	rate	# Events	# Patients	rate
All adverse events	15	15	14.85%	13	11	11.11%
Adverse events leading to discontinuation	0	0	0	0	0	0
Adverse reactions*	7	7	6.93%	2	2	2.02%
Adverse reactions leading to discontinuation	0	0	0	0	0	0

Individual reported adverse events sre shown in the table below.

Table 15-9 Preferred Terms and Frequency of Adverse Reaction

Name of adverse reaction	Norvasc (103 patients)		[redacted] (b) (4) (101 patients)	
	Number	Frequency (%)	Number	Frequency (%)
Both lower extremities/ankle edema/dropsy edema peripheral	3	2.91%	0	0
Liver function test abnormal	1	0.97%	0	0
Abdominal discomfort	1	0.97%	0	0
Dizziness	1	0.97%	2	1.98%
Palpitation	1	0.97%	0	0

Reported adverse events are similar between the two treatment groups.

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/s/

MARYANN GORDON
11/01/2019 10:23:12 AM

KAREN A HICKS
11/05/2019 07:53:02 PM