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ORIGINAL ARTICLE

Efficacy and safety of losartan 100 mg/ hydrochlorothiazide 12.5 mg in Japanese subjects with essential hypertension: two randomized, controlled trials

This article has been corrected since Advance Online Publication, and a corrigendum is also printed in this issue.

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Two randomized studies were designed to assess the safety, tolerability and efficacy of losartan 100 mg (L100) plus hydrochlorothiazide 12.5 mg (H12.5) in a single fixed-dose combination. In one study, subjects received losartan 50 mg (L50) plus H12.5 during an 8-week filter period. They were then randomized to either L100/H12.5 or L50/H12.5 for another 8 weeks, followed by L100/H12.5 for 44 weeks. The primary end point was safety of L100/H12.5 for 52 weeks. In the second study, subjects received L100 during an 8-week filter period. Subjects were then randomized to receive either L100/H12.5 or L100 for a further 8 weeks. The primary end point was change from baseline in sitting diastolic blood pressure (SiDBP) at week 8. Safety was assessed throughout both studies. L100/H12.5 reduced SiDBP and sitting systolic blood pressure (SiSBP) at 8 weeks, and when compared with L100, the differences were statistically significant for both measures ($P<0.001$). L100/H12.5 reductions SiDBP for 8 weeks were comparable to L50/H12.5. The efficacy of L100/H12.5 was maintained to week 52. Drug-related adverse events with an incidence $\geqslant$2% in the L100/H12.5 group during the 52-week extension period were an increase in aspartate aminotransferase and in blood uric acid. Additionally, mean uric acid levels were reduced by 0.57 mg dl^{-1} from baseline with long-term treatment with L100/H12.5 in subjects whose baseline uric acid level was $>$7.0 mg dl^{-1}. In conclusion, L100/H12.5 was shown to be more effective than L100 at reducing SiDBP and SiSBP and showed good tolerability in Japanese patients with essential hypertension.
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Keywords: hydrochlorothiazide; Japanese; losartan; randomized; uric acid

INTRODUCTION

It is estimated that hypertension currently affects 43 million people in Japan, and this prevalence is predicted to increase as the population ages.[1] As hypertension is a major risk factor for developing cardiovascular, cerebrovascular and renal disease, if left untreated, associated conditions can incur very high medical expenditures, primarily due to the cost of hospitalization.[2]

For patients with essential hypertension inadequately controlled by a single agent, the Japanese Society of Hypertension treatment guidelines recommend either increasing the dose of the current antihypertensive agent or co-administering a different type of agent.[1] As increasing the dose of a single agent can increase the risk of side effects, often without a proportionate reduction in blood pressure (BP), combination therapy using agents with complementary mechanisms of action is frequently the preferred option. The most commonly prescribed antihypertensive agents in Japan include calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and diuretics. However, by increasing the number of unit doses that need to be taken, either by increasing doses and/or introducing additional antihypertensive treatments, problems with decreasing compliance can occur.[3] Fixed-dose combinations have the advantage of delivering multiple treatments in a single dosage form and have been shown to improve both adherence to treatment and achievement of BP targets.[4]

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A fixed-dose combination of losartan potassium 50 mg (L50), an angiotensin II receptor blocker, and hydrochlorothiazide 12.5 mg (H12.5), a thiazide diuretic, was approved as PREMINENT LD (Merck, Whitehouse Station, NJ, USA) in Japan in 2006. The higher-dose combination of losartan 100 mg (L100)/H12.5 (MK-0954A) has also been approved as PREMINENT HD (Merck) in Japan in 2013. This publication reports the antihypertensive efficacy, safety and tolerability of L100/H12.5 therapy compared with L50/H12.5 or L100 therapy (based on the step-wise treatment options for L100/H12.5) as assessed in two randomized studies of Japanese subjects with essential hypertension.

METHODS

Ethics statement

Both studies were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Both protocols were approved by local institutional review boards, and all subjects provided written, informed consent before initiation of the studies. The trials were designed by MSD KK, Tokyo, Japan. Statistical analyses were performed by the Clinical Biostatistics department of MSD KK, and the authors were responsible for checking the accuracy and completeness of the data and all analyses.

Study design

The first study (L50/H12.5 filter study) was a two-part trial in Japanese subjects with essential hypertension (Protocol MK0954A-351; ClinicalTrials.gov identifier NCT01307033), comprising an 8-week, double-blind, randomized, active-comparator controlled period followed by an open-label 44-week extension. The study was conducted in 35 centers in Japan between April 2011 and December 2012.

During an 8-week filter period, subjects with previous antihypertensive therapy were treated with L50/H12.5 (plus matching placebo for L100/H12.5). Eligible subjects were then randomized to L100/H12.5 or L50/H12.5 for 8 weeks. During the extension period, all eligible subjects received L100/H12.5 for 44 weeks. After week 12, other antihypertensive agents were permitted at the investigator's discretion if the subject's sitting systolic BP (SiSBP) was >140 mm Hg and/or their sitting diastolic BP (SiDBP) was >90 mm Hg. If a subject received any other antihypertensive agent, then the BP measurements taken after the introduction of other agents were excluded from the long-term efficacy analyses.

The second study (L100 filter study) was a randomized, double-blind, active-comparator controlled, Phase III multicenter trial (Protocol MK0954A-352; ClinicalTrials.gov identifier NCT01307046) also in Japanese subjects with essential hypertension. This study was conducted in 29 centers in Japan between March 2011 and February 2012. Treatment-naive subjects received L50 plus matching placebo for L100 for 4 weeks, if appropriate (see inclusion criteria); they were then treated with L100 plus matching placebo for L50 for an additional 4 weeks. Subjects with previous antihypertensive therapy were treated with L100 plus matching placebo for L50 during the 8-week filter period. Eligible subjects were then randomized to double-blind treatment with either L100 or L100/H12.5 for 8 weeks.

In both studies, eligible subjects discontinued any previous antihypertensive medication the day before beginning the single-blind, 8-week filter period. Physicians were given discretion to taper off medications, according to their clinical judgment and the package circulars. Subjects who were eligible for entry into the 8-week double-blind period were randomized in a 1:1 ratio. All treatments were administered orally once-daily in the morning.

Subjects

Japanese male and female outpatients aged between 20 and 80 years, with a diagnosis of essential hypertension and who were considered by the investigator to be suitable to receive the filter period treatment were eligible for inclusion in either trial. Subjects were eligible for inclusion in the double-blind period of either trial if they had been compliant with taking the filter medication and had inadequate control of BP with L50/H12.5 (L50/H12.5 filter study) or L100 (L100 filter study), defined as mean trough SiDBP 90–110 mm Hg and SiSBP 140–180 mm Hg at the end of filter period, and a mean difference between weeks 4 and 8 of the filter period of $\leqslant 10$ mm Hg in SiDBP and $\leqslant 20$ mm Hg in SiSBP.

Subjects were excluded from the studies if they were taking more than three antihypertensive medications, had secondary hypertension of any etiology, malignant hypertension, history of stroke or cardiovascular diseases (for example, angina or myocardial infarction) within 6 months, serious cardiovascular disorders, renal or hepatic dysfunction, type 1 diabetes or inadequately controlled type 2 diabetes, gout and/or hyperuricemia requiring drug treatment or a clinically significant blood disorder. Female subjects of childbearing potential were required to agree to remain abstinent or use suitable contraception for the duration of the study.

Randomization and blinding

Randomization was stratified by study center. The study sponsor (Merck, Whitehouse Station, NJ, USA) generated the 1:1, double-blind allocation schedule in accordance with its standard operating procedure. The allocation schedule was strictly retained until completion of the study. Medication compliance was assessed by subject reports and confirmed by a tablet count at all visits, starting at the filter visit. Subjects were required to maintain at least 75% compliance during the filter period to continue into the double-blind portion of the study.

End points

The primary end point of the L50/H12.5 filter study was the safety and tolerability of L100/H12.5 for up to 52 weeks. The secondary end point was the change from baseline to week 8 in mean trough SiDBP and SiSBP. An exploratory end point was the change from baseline in mean trough SiDBP and SiSBP through 52 weeks of treatment with L100/H12.5. The primary end point of the L100 filter study was the change from baseline in mean trough SiDBP at week 8. The secondary end point was change from baseline in mean trough SiSBP at week 8.

Safety

Safety assessments included adverse events (AEs), discontinuation rate, laboratory safety tests and vital signs. The following events were prespecified AEs of interest: hypotension reported as an AE; asymptomatic BP decrease (SiDBP by >15 mm Hg or SiSBP by >30 mm Hg from previous measurement); orthostatic hypotension (change from sitting to standing BP measurement is >20 mm Hg systolic or >10 mm Hg diastolic with symptoms); dizziness; syncope; worsening renal function (increase in serum creatinine >0.5 mg dl^{-1} from baseline); serum potassium >5.5 mEq l^{-1} and an increase in serum potassium >0.5 mEq l^{-1} from baseline; serum potassium <3.5 mEq l^{-1} and a decrease in serum potassium from baseline of >0.5 mEq l^{-1}; serum sodium <125 mEq l^{-1}; consecutive elevations in aspartate aminotransferase or alanine transaminase $>3\times$ upper limit of normal; and serum uric acid >8.4 mg dl^{-1} and elevation by 20% from baseline. Sitting BP and heart rate, orthostatic BP and heart rate and weight were monitored throughout both the studies.

Statistical analysis

For both studies, the efficacy analyses during the double-bind period were performed on the full analysis set (FAS) population, using the constrained longitudinal data analysis model by Liang and Zeger,[5] with terms for treatment, time and treatment-by-time interaction. The FAS population was defined as all randomized subjects who received at least one dose of study treatment and had at least one postrandomization observation for the analysis end point.

The safety analyses were performed on the all subjects as treated (ASaT) population, consisting of all randomized subjects who received at least one dose of study treatment. Prespecified safety parameters or AEs of interest were subject to inferential testing for statistical significance, with *P*-values and 95% confidence intervals (CIs) provided for between-group comparisons. For between-treatment differences in the percentage of subjects with respective events, *P*-values and 95% CI were calculated using the Miettinen and Nurminen method.[6]

For the L50/H12.5 filter study, the mean and s.e. for within-group change from baseline in trough SiDBP and SiSBP at each time point during the extension period was calculated. The data for BP values of subjects with other antihypertensive agents added during the extension period were excluded from the FAS population. The study was not powered to test for statistical significance in between-treatment BP reduction.

The L100 filter study aimed to randomize 326 subjects and to detect between-treatment differences with 90% power (significance level of 0.05) of change in SiDBP (−2.9 mm Hg; s.d. estimate 7.6 mm Hg). The calculation was based on the inverse probability weighted complete cases approach by Lu *et al.*,[7] assuming an overall discontinuation rate of 10%.

RESULTS

Subjects

Subject flow through the L50/H12.5 filter study is shown in Figure 1a. A total of 649 subjects were screened, 278 of whom were randomized to receive L100/H12.5 ($n=134$) or L50/H12.5 ($n=144$) in the 8-week double-blind period and were included in the FAS and ASaT double-blind period analyses. The baseline characteristics were generally similar between the treatment groups (Table 1). The majority of subjects in both the treatment groups (L50/H12.5 *vs.* L100/H12.5) were male (71.5% *vs.* 76.1%), aged <65 years (77.1% *vs.* 73.9%) and had a baseline SiDBP <100 mm Hg (75.7% *vs.* 84.3%). A total of 258 subjects continued to the 52-week extension period and were included in the FAS and ASaT extension period analyses. Of these subjects, 114 (44.2%) received other antihypertensive agents during the extension period, most commonly amlodipine. Baseline characteristics of subjects who received additional antihypertensive agents during the extension period are summarized in Supplementary Table S1.

Subject flow through the L100 filter study is shown in Figure 1b. A total of 336 subjects were randomized to receive L100/H12.5 ($n=166$) or L100 ($n=170$) in the 8-week double-blind phase. One subject in the L100 group was randomized twice and was therefore excluded from the efficacy analysis. Subject baseline characteristics were generally similar between the two treatment groups (Table 1). The majority of subjects in both the treatment groups (L100 *vs.* L100/H12.5) were male (64.7% *vs.* 77.7%), aged <65 years (84.7% *vs.* 83.1%) and had a baseline SiDBP <100 mm Hg (64.7% *vs.* 69.3%).

Efficacy

In the L50/H12.5 filter study, the differences between L100/H12.5 and L50/H12.5 in change from baseline to week 8 for SiDBP was 0.2 mm Hg (95% CI: −1.7, 2.2) (Table 2, Figure 2a) and for SiSBP was −2.3 mm Hg (95% CI: −5.0, 0.5) (Table 2, Figure 2b). Differences at weeks 2 and 4 are shown in Table 2. When comparing L50/H12.5 with L100/H12.5 through all time points (weeks 2, 4 and 8) for mean change from baseline in SiDBP and SiSBP, *P*-values were 0.6590 and 0.0317, respectively. The efficacy of L100/H12.5 was sustained over 52 weeks of treatment in the FAS population (Figure 2).

In the L50/H12.5 filter study, all subjects ($n=124$) who completed 52 weeks without other antihypertensive agents (non-add-on group), the changes from baseline (s.d.) at week 52 were −11.34 (7.89) mm Hg for SiDBP and −16.40 (10.71) mm Hg for SiSBP; and in the L100/H12.5 non- add-on group at week 8 ($n=59$) were −8.47 (8.42) mm Hg for SiDBP (Supplementary Figure S1a, Supplementary Table S2) and −12.50 (11.64) mm Hg for SiSBP (Figure 3a, Supplementary Table S2). In all subjects ($n=114$) who completed 52 weeks while also taking other antihypertensive agents (add-on group), the changes from baseline at week 52 were −11.21 (8.07) mm Hg for SiDBP (Supplementary Figure S1b, Supplementary Table S3) and −16.22 (12.54) mm Hg for SiSBP; and in the L100/H12.5 add-on group ($n=57$) at week 8 were −2.14 (5.87) mm Hg for SiDBP and −4.96 (9.72) mm Hg for SiSBP (Figure 3b and Supplementary Table S3).

In the L100 filter study, the differences between L100/H12.5 and L100 in change from baseline to week 8 for SiDBP was −5.1 mm Hg

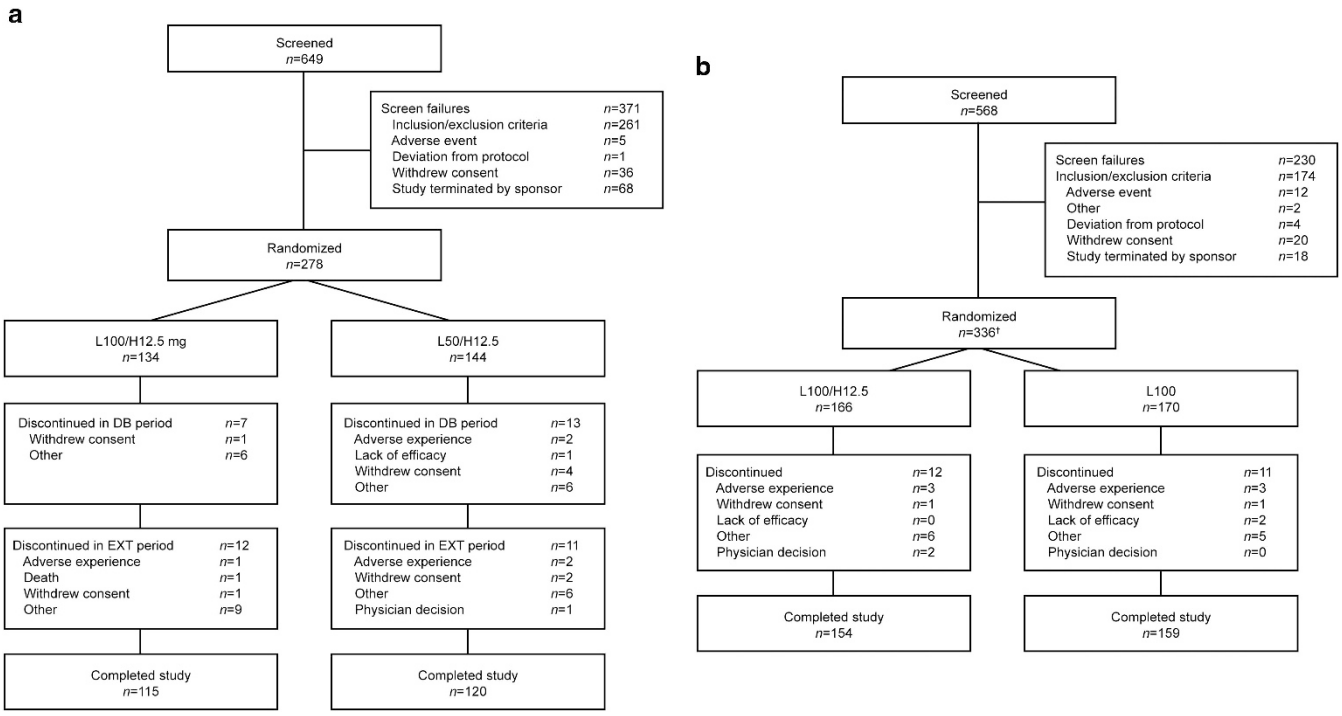

Figure 1 Subject flow through the studies. (**a**) L50/H12.5 filter study. (**b**) L100 filter study. †One subject who was randomized twice in the L100 group was not included. DB, double blind; EXT, Extension; H12.5, hydrochlorothiazide 12.5 mg; L50, losartan 50 mg; L100, losartan 100 mg.

Table 1 Subject demographics and baseline characteristics (full analysis set population)

	L50/H12.5 filter study		*L100 filter study*	
	L50/H12.5 (n = *144*)	*L100/H12.5* (n = *134*)	*L100* (n = *170*)	*L100/H12.5* (n = *166*)
Gender—n (%)				
Male	103 (71.5)	102 (76.1)	110 (64.7)	129 (77.7)
Female	41 (28.5)	32 (23.9)	60 (35.3)	37 (22.3)
Age (years)—mean (s.d.)	56.9 (10.7)	57.8 (10.8)	54.9 (9.5)	55.7 (9.2)
<65 years—*n* (%)	111 (77.1)	99 (73.9)	144 (84.7)	138 (83.1)
⩾65 years—*n* (%)	33 (22.9)	35 (26.1)	26 (15.3)	28 (16.9)
Body mass index (kg m^{-2})—mean (s.d.)	26.1 (3.7)	25.9 (3.7)	26.3 (3.7)	26.8 (4.8)
Baseline SiDBP—n (%)				
<100 mm Hg	109 (75.7)	113 (84.3)	110 (64.7)	115 (69.3)
⩾100 mm Hg	35 (24.3)	21 (15.7)	60 (35.3)	51 (30.7)
Type 2 diabetes—*n* (%)	30 (20.8)	25 (18.7)	17 (10.0)	22 (13.3)
Dyslipidemia—*n* (%)	57 (39.6)	58 (43.3)	57 (33.5)	71 (42.8)
Years of hypertension—mean (s.d.)	6.7 (6.1)	7.1 (6.8)	5.8 (6.8)	6.2 (6.6)
No. of antihypertensive medications—n (%)				
0	0 (0.0)	0 (0.0)	44 (25.9)	33 (19.9)
1	57 (39.6)	45 (33.6)	86 (50.6)	83 (50.0)
2	87 (60.4)	89 (66.4)	40 (23.5)	50 (30.1)
Renal function stage—n (%)				
G1 (>90): normal or high eGFR value	17 (11.8)	21 (15.7)	26 (15.3)	29 (17.5)
G2 (60–89): normal or mildly reduced function	99 (68.8)	91 (67.8)	114 (67.1)	113 (68.1)
G3a (45–59): mildly to moderately reduced function	20 (13.9)	21 (15.7)	28 (16.5)	23 (13.9)
G3b (30–44): moderately to severely reduced function	8 (5.6)	1 (0.7)	2 (1.2)	1 (0.6)

Abbreviations: eGFR, estimated glomerular filtration rate; H12.5, hydrochlorothiazide 12.5 mg; L50, losartan 50 mg; L100, losartan 100 mg; SiDBP, sitting diastolic blood pressure.

(95% CI: −6.8, −3.4; $P<0.001$) and for SiSBP was −9.2 mm Hg (95% CI: −11.9, −6.5; $P<0.001$) (Table 2, Supplementary Figure S2).

Safety

The percentage of subjects with AEs, drug-related AEs and discontinuation due to AEs were similar across the two studies. A summary of the AE profile at week 8 in both studies and at week 52 in the L50/H12.5 filter study is shown in Supplementary Table S4. In the L50/H12.5 filter study, AEs reported by ⩾2% of subjects over the 52 weeks are shown in Table 3. The most commonly reported clinical AEs (*n* (%)) were nasopharyngitis (55 (20.8)), upper respiratory tract infection and increase in blood uric acid (both 17 (6.4)). None of these were considered related to drug except blood uric acid increased. Drug-related AEs with an incidence of ⩾2.0% in the L100/H12.5 group during the 52-week extension period were an increase in aspartate aminotransferase and blood uric acid, both of which are reported by 2.2% (3/134) of subjects. There was one drug-related serious AE reported, a cerebral infarction that occurred on day 340 and was determined as having resolved with sequelae when the subject was discharged. One subject died due to a pulmonary embolism during the study; this was considered probably not drug-related by the investigator.

There was no statistically significant difference between the treatment groups in terms of subjects experiencing any prespecified AEs of interest (Supplementary Table S5a). The mean baseline (s.d.) uric acid in the L100/H12.5 group ($n=238$) was 6.61 (1.58) mg dl^{-1} and the change from baseline at 52 weeks was −0.37 (1.09) mg dl^{-1}. Thirteen subjects who used uric acid-lowering agents were excluded. In order to confirm the uric acid effect, a *post-hoc* analysis was performed. In subjects with uric acid baseline levels ⩽7 mg dl^{-1} without uric acid-lowering agents ($n=144$), the mean baseline (s.d.) uric acid level was 5.60 (0.98) mg dl^{-1} and the change from baseline at 52 weeks was −0.08 (0.82) mg dl^{-1} (95% CI: −0.21, 0.06). In the subject group with mean uric acid baseline levels >7 mg dl^{-1} without uric acid-lowering agents ($n=81$), the mean baseline uric acid (s.d.) level was 8.00 (0.85) mg dl^{-1} and the change from baseline at 52 weeks was −0.57 (0.94) mg dl^{-1} (95% CI: −0.78, −0.37, $P<0.001$) (Supplementary Table S6).

Similar to the L50/H12.5 filter study, the only drug-related AE with an incidence of ⩾2.0% in the L100 filter study was an increase in blood uric acid (L100 group: 0% (0/170 subjects) and L100/H12.5 group: 2.4% (4/166 subjects)). The mean baseline (s.d.) uric acid was 5.56 (1.30) mg dl^{-1} in the L100 group and 5.73 (1.27) mg dl^{-1} in the L100/H12.5 group. The change from baseline at 8 weeks was −0.04 (0.64) mg dl^{-1} in the L100 group ($n=159$) and 0.46 (0.71) mg dl^{-1} in the L100/H12.5 group ($n=157$).

No deaths or serious AEs were observed in either group. There was a statistically significant difference in AEs of interest between the two treatment groups in terms of subjects experiencing a decrease

Table 2 Change from baseline in mean trough SiDBP and SiSBP (mm Hg)

		SiDBP: change from baseline: LS mean (s.e.)[a]		
Dose groups	*Sample size*	*Week 2*	*Week 4*	*Week 8*
L50/H12.5 filter study (FAS population)				
L100/H12.5	134	−4.7 (0.6)	−5.7 (0.7)	−5.0 (0.7)
(95% CI)		(−6.0, −3.5)	(−7.0, −4.4)	(−6.4, −3.6)
L50/H12.5	144	−4.2 (0.6)	−5.0 (0.6)	−5.3 (0.7)
(95% CI)		(−5.4, −3.0)	(−6.2, −3.7)	(−6.6, −3.9)
Difference in LS mean (95% CI)[a]		−0.5 (−2.3, 1.2)	−0.7 (−2.5, 1.1)	0.2 (−1.7, 2.2)
(L100/H12.5 group *vs.* L50/H12.5 group)				
L100 filter study (FAS population)				
L100/H12.5	166	−6.8 (0.5)	−8.7 (0.6)	−8.7 (0.6)
(95% CI)		(−7.9, −5.8)	(−9.8, −7.5)	(−9.9, −7.6)
L100	170	−3.3 (0.5)	−4.8 (0.6)	−3.6 (0.6)
(95% CI)		(−4.4, −2.2)	(−6.0, −3.7)	(−4.8, −2.5)
Difference in LS mean (95% CI)[a]		−3.5 (−5.1, −2.0)	−3.8 (−5.5, −2.2)	−5.1 (−6.8, −3.4)
(L100/H12.5 group *vs.* L50/H12.5 group)				
		SiSBP: Change from baseline: LS mean (s.e.)[a]		
		Week 2	*Week 4*	*Week 8*
L50/H12.5 filter study (FAS population)				
L100/H12.5	134	−6.3 (0.9)	−7.9 (0.9)	−8.5 (1.0)
(95% CI)		(−8.1, −4.5)	(−9.6, −6.1)	(−10.5, −6.5)
L50/H12.5	144	−3.8 (0.9)	−5.8 (0.9)	−6.2 (1.0)
(95% CI)		(−5.6, −2.1)	(−7.5, −4.1)	(−8.2, −4.3)
Difference in LS mean (95% CI)[a]		−2.5 (−5.0, 0.1)	−2.1 (−2.5, 1.1)	−2.3 (−5.0, 0.5)
(L100/H12.5 group *vs.* L50/H12.5 group)				
L100 filter study (FAS population)				
L100/H12.5	166	−11.4 (0.8)	−14.7 (0.9)	−14.5 (1.0)
(95% CI)		(−13.0, −9.7)	(−16.4, −13.0)	(−16.5, −12.6)
L100	170	−4.3 (0.8)	−6.3 (0.9)	−5.4 (1.0)
(95% CI)		(−5.9, −2.6)	(−8.0, −4.6)	(−7.3, −3.4)
Difference in LS mean (95% CI)[a]		−7.1 (−9.4, −4.8)	−8.4 (−10.7, −6.0)	−9.2 (−11.9, −6.5)
(L100/H12.5 group *vs.* L50/H12.5 group)				

Abbreviations: CI, confidence interval; FAS, full analysis set; H12.5, hydrochlorothiazide 12.5 mg; LS, least square; L50, losartan 50 mg; L100, losartan 100 mg; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure.
P-values for between-treatment comparisons for SiDBP in the L50/H12.5 filter study are 0.5531, 0.4280, 0.8018 and 0.6590 for Week 2, Week 4, Week 8 and through all time points, respectively.
P-values for between-treatment comparisons for SiSBP in the L50/H12.5 filter study are 0.0565, 0.0910, 0.1061 and 0.0317 for Week 2, Week 4, Week 8 and through all time points, respectively.
All *P*-values for between-treatment comparisons for SiDBP and SiSBP in the L100 filter study are <0.001 for Week 2, Week 4, Week 8 and through all time points.
[a]Computed using a constrained longitudinal data analysis model, including treatment, time and the interaction of time by treatment with a restriction of the same baseline mean across the treatment groups.

in BP (34/166 (20.5%) in the L100/H12.5 group *vs.* 18/170 (10.6%) in the L100 group, $P=0.012$) and uric acid $>8.4\,mg\,dl^{-1}$ and elevation by $>20\%$ from baseline (7/166 (4.2%) in the L100/H12.5 group *vs.* 0/170 (0%) in the L100 group, $P=0.007$) (Supplementary Table S5b). The mean baseline values of uric acid for seven subjects in the L100/H12.5 group were $7.4\,mg\,dl^{-1}$ (baseline range: 6.6–8.5).

DISCUSSION

In the L50/H12.5 filter study, L100/H12.5 did not show a potent antihypertensive effect compared with L50/H12.5 at 8 weeks. However, approximately half of the subjects who completed 52 weeks of treatment managed their BP with L100/H12.5 only (non-add-on group), and for this population (non-add-on group), the mean change from baseline at 8 weeks in the L100/H12.5 group was numerically more effective than the L50/H12.5 group. In addition, the mean change from baseline at 52 weeks in SiDBP and SiSBP for the non-add-on group subjects was comparable with the subjects who completed 52 weeks with additional antihypertensive treatment (add-on group). Although there were no clear differences in subject characteristics between the non-add-on group and the add-on group, the baseline SiDBP and SiSBP in the non-add-on group was slightly less than the add-on group. Further investigation will be needed to ascertain which characteristics are affected in response to treatment with L100/H12.5. The safety and tolerability of L100/H12.5 were favorable and comparable to L50/H12.5, and long-term analysis demonstrated that L100/H12.5 was generally well tolerated. In addition, the mean uric acid levels were reduced by $0.57\,mg\,dl^{-1}$

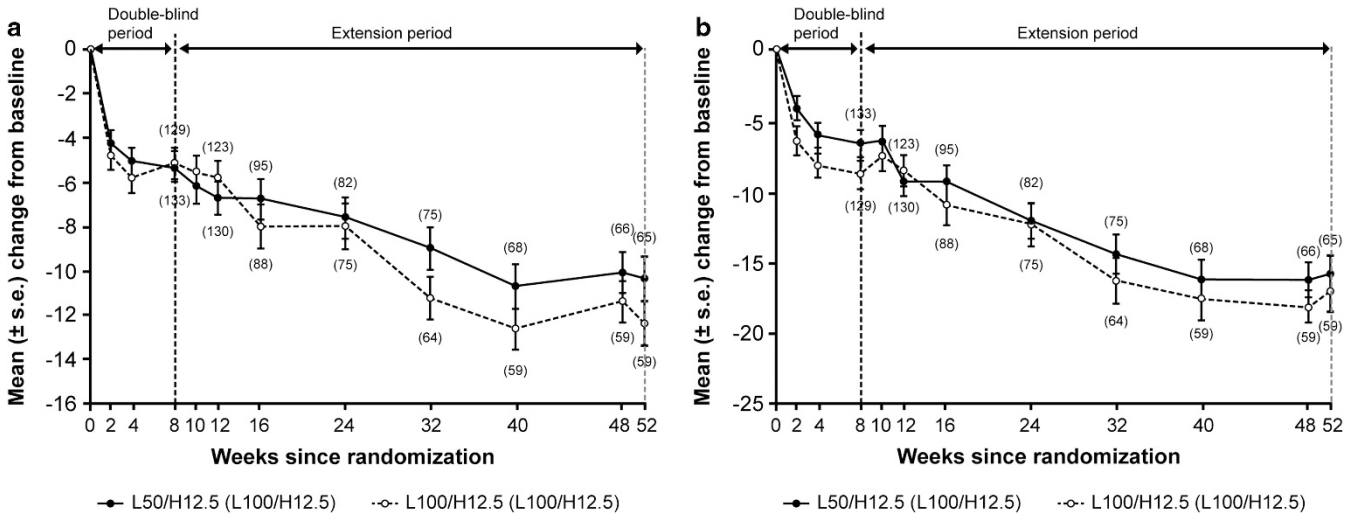

Figure 2 Mean change from baseline in (**a**) sitting diastolic blood pressure (SiDBP) and (**b**) sitting systolic blood pressure (SiSBP) over 52 weeks in the L50/H12.5 filter study (full analysis set (FAS) population). (**a**) SiDBP. (**b**) SiSBP. H12.5, hydrochlorothiazide 12.5 mg; L50; losartan 50 mg; L100, losartan 100 mg The solid line shows time course of mean blood pressure in subjects who received L50/H12.5 in the double-blind (DB) period and L100/H12.5 in the extension period. The dotted line shows time course of mean blood pressure in subjects received L100/H12.5 in the DB period and L100/H12.5 in the extension period. After week 12, other antihypertensive agents were permitted at the investigator's discretion if the subject's SiSBP was >140 mm Hg and/or their SiDBP was >90 mm Hg. If a subject received any other antihypertensive agent, then the BP measurements taken after the introduction of other agents were excluded from the long-term efficacy analyses.

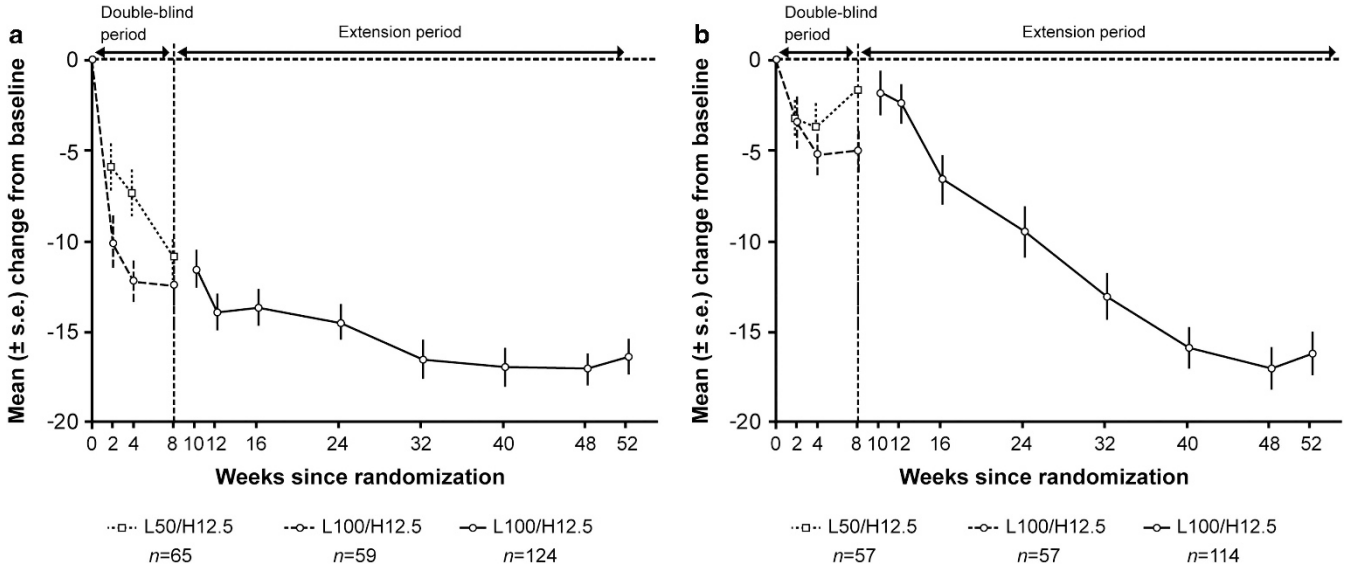

Figure 3 Mean change from baseline in sitting systolic blood pressure (SiSBP) over 52 weeks in (**a**) subjects who did not use concomitant antihypertensive medication (non-add-on group) and (**b**) subjects who had additional antihypertensive medication (add-on group) during the extension period of the L50/H12.5 filter study. (**a**) Non-add-on group. (**b**) Add-on group. H12.5, hydrochlorothiazide 12.5 mg; L100, losartan 100 mg.

from baseline with long-term treatment of L100/H12.5, in subjects whose baseline uric acid level was $>7.0\,mg\,dl^{-1}$. These results suggest that an additional antihypertensive effect from L50/H12.5 to L100/H12.5 is small. However, long-term treatment with L100/H12.5 reduced serum uric acid, and there is a definite responder group with L100/H12.5, as shown by the lack of additional antihypertensive effect between the add-on group and non-add-on group after 52 weeks of treatment.

In the L100 filter study, L100/H12.5 showed a potent antihypertensive effect compared with L100 at 8 weeks. There was a higher incidence of drug-related increases in serum uric acid, uric acid $>8.4\,mg\,dl^{-1}$ and uric acid elevation by >20% from baseline in the L100/H12.5 group compared with the L100 group. Although the mean change from baseline in uric acid with the addition of H12.5 was small and remained within the normal range, consideration of this change in uric acid levels is warranted in the clinical setting.

The L50/H12.5 filter study suggests that L100/H12.5 potentially has the effect of lowering serum uric acid for subjects whose baseline serum uric acid is $>7.0\,mg\,dl^{-1}$ and uncontrolled with L50/H12.5,

Table 3 Number (%) of subjects experiencing adverse events (incidence ⩾2%) overall and drug-related over 52 weeks in L50/H12.5 filter study (all subjects as treated population)

	L50/H12.5 (L100/H12.5)		*L100/H12.5 (L100/H12.5)*		*Total*	
	Overall n (%)	*Drug related[a] n (%)*	*Overall n (%)*	*Drug related[a] n (%)*	*Overall n (%)*	*Drug related[a] n (%)*
Subjects in population	131	131	134	134	265	265
With ⩾1 adverse events	93 (71.0)	14 (10.7)	97 (72.4)	18 (13.4)	190 (71.7)	32 (12.1)
Atrial fibrillation	3 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)
Back pain	3 (2.3)	0 (0.0)	4 (3.0)	0 (0.0)	7 (2.6)	0 (0.0)
Bronchitis	4 (3.1)	0 (0.0)	3 (2.2)	0 (0.0)	7 (2.6)	0 (0.0)
Diabetes mellitus	7 (5.3)	0 (0.0)	5 (3.7)	0 (0.0)	12 (4.5)	0 (0.0)
Eczema	2 (1.5)	0 (0.0)	3 (2.2)	0 (0.0)	5 (1.9)	0 (0.0)
Gastritis	6 (4.6)	0 (0.0)	3 (2.2)	1 (0.7)	9 (3.4)	1 (0.4)
Gastroenteritis	2 (1.5)	0 (0.0)	5 (3.7)	0 (0.0)	7 (2.6)	0 (0.0)
Gastroesophageal reflux disease	3 (2.3)	0 (0.0)	2 (1.5)	0 (0.0)	5 (1.9)	0 (0.0)
Headache	3 (2.3)	0 (0.0)	2 (1.5)	0 (0.0)	5 (1.9)	0 (0.0)
Hyperuricemia	3 (2.3)	2 (1.5)	4 (3.0)	2 (1.5)	7 (2.6)	4 (1.5)
Musculoskeletal stiffness	1 (0.8)	0 (0.0)	3 (2.2)	1 (0.7)	4 (1.5)	1 (0.4)
Nasopharyngitis	22 (16.8)	0 (0.0)	33 (24.6)	0 (0.0)	55 (20.8)	0 (0.0)
Osteoarthritis	1 (0.8)	0 (0.0)	3 (2.2)	0 (0.0)	4 (1.5)	0 (0.0)
Pharyngitis	4 (3.1)	0 (0.0)	4 (3.0)	0 (0.0)	8 (3.0)	0 (0.0)
Rash	1 (0.8)	0 (0.0)	3 (2.2)	0 (0.0)	4 (1.5)	0 (0.0)
Rhinitis	4 (3.1)	0 (0.0)	1 (0.7)	0 (0.0)	5 (1.9)	0 (0.0)
Rhinitis allergic	2 (1.5)	0 (0.0)	3 (2.2)	0 (0.0)	5 (1.9)	0 (0.0)
Seasonal allergy	3 (2.3)	0 (0.0)	3 (2.2)	0 (0.0)	6 (2.3)	0 (0.0)
Upper respiratory tract infection	10 (7.6)	0 (0.0)	7 (5.2)	0 (0.0)	17 (6.4)	0 (0.0)
Upper respiratory tract inflammation	7 (5.3)	0 (0.0)	5 (3.7)	0 (0.0)	12 (4.5)	0 (0.0)
Vertigo	3 (2.3)	0 (0.0)	2 (1.5)	0 (0.0)	5 (1.9)	0 (0.0)
Laboratory values						
Alanine aminotransferase increased	2 (1.5)	0 (0.0)	5 (3.7)	2 (1.5)	7 (2.6)	2 (0.8)
Aspartate aminotransferase increased	2 (1.5)	0 (0.0)	4 (3.0)	3 (2.2)	6 (2.3)	3 (1.1)
Blood creatinine increased	4 (3.1)	0 (0.0)	5 (3.7)	2 (1.5)	9 (3.4)	2 (0.8)
Blood potassium decreased	4 (3.1)	2 (1.5)	1 (0.7)	0 (0.0)	5 (1.9)	2 (0.8)
Blood uric acid increased	6 (4.6)	4 (3.1)	11 (8.2)	3 (2.2)	17 (6.4)	7 (2.6)
Brain natriuretic peptide increased	2 (1.5)	2 (1.5)	3 (2.2)	1 (0.7)	5 (1.9)	3 (1.1)
Urine albumin/creatinine ratio increase	3 (2.3)	1 (0.8)	1 (0.7)	0 (0.0)	4 (1.5)	1 (0.4)

Abbreviations: H12.5, hydrochlorothiazide 12.5 mg; L50, losartan 50 mg; L100, losartan 100 mg.
Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in ⩾1 of the 'Overall' columns meets the incidence criterion in the report title, after rounding.
The L50/H12.5 (L100/H12.5) group includes data only from extension period (44 weeks); L100/H12.5 (L100/H12.5) group includes data from entire study period (52 weeks).
[a]Determined by the investigator to be related to the drug.

while the L100 filter study demonstrated that L100/H12.5 was more effective than L100 at lowering SiDBP and SiSBP after 8 weeks of treatment.

There were some limitations to this study. The 52-week extension phase was open-label, and therefore subjects were not blinded to treatment. In addition, the population was a convenient sample of subjects to increase the length of treatment. A larger, randomized sample of subjects may allow safety results to be better generalized. Another limitation was that the study ended after 52 weeks of treatment, but in routine clinical practice the majority of subjects will take antihypertensive medications for many years. Finally, the L50/H12.5 filter was not powered to test for statistical significance in SiDBP and SiSBP reduction between treatments. Therefore, the efficacy results should be interpreted with caution. In conclusion, L100/H12.5 was shown to be more effective than L100 at reducing SiDBP and SiSBP and showed good tolerability up to 52 weeks in Japanese subjects with essential hypertension.

CONFLICT OF INTEREST

HR received honoraria and/or fees for promotional materials from Astellas Pharma, Daiichi Sankyo, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim, Novartis Pharma and Takeda Pharmaceutical and received research funding from Astellas Pharma, Daiichi Sankyo, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, MSD KK, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan and Takeda Pharmaceutical. TT received honoraria and/or fees for promotional materials from Dainippon-Sumitomo and MSD KK and received research funding from MSD KK. KS received honoraria and/or fees for promotional materials from Daiichi Sankyo, Dainippon-Sumitomo, MSD KK, Novartis and Takeda Pharmaceutical. HN, CN, HY, GF, KA and MS are employees of MSD KK. MEH and KF are employees of Merck and may own stock or hold stock options in the company.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)