

Effectiveness and Safety of Telmisartan Plus Amlodipine Compared to Telmisartan Plus Cilnidipine in Indian Patients with Hypertension and Renal Impairment: A Randomized, Open Label, Post Marketing Study (START Renal)

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Purpose: To assess the effectiveness and safety of telmisartan-amlodipine (TA) versus telmisartan-cilnidipine (TC) fixed-dose combinations (FDCs) in patients with hypertension and renal impairment.

Patients and Methods: This open label, randomized, multicentric, post-marketing study was conducted in India. Adult patients with hypertension and renal impairment, receiving a stable dose of telmisartan and not on calcium channel blockers, were enrolled. Participants were randomized (1:1) to receive the TA or TC FDC for 12 months. The primary endpoint was change in the urine albumin-creatinine ratio (UACR) from baseline to 12 months. Secondary endpoints included changes in estimated glomerular filtration rate (eGFR), serum creatinine, and serum uric acid at 6 and 12 months, and office systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 3, 6, 9, and 12 months. Similar parameters were assessed in the diabetic subpopulation. Adverse events were recorded and classified using system organ classification.

Results: At 12 months, the TA and TC groups showed significant reductions in UACR by 119 ± 157.7 mg/g and 97.5 ± 128.6 mg/g, respectively ($p < 0.0001$ for both). Improvements in eGFR and serum creatinine were comparable between groups ($p > 0.05$). SBP reduction was significantly greater with TA at both 9 months (20.74 ± 12.75 vs. 16.9 ± 13.66 mmHg, ($p = 0.0430$)) and 12 months (25.4 ± 14.25 vs. 20.6 ± 10.94 mmHg, ($p = 0.0397$)), while DBP reductions were similar. The diabetic subgroup showed a superior SBP reduction favoring the TA group -24.5 (± 13.75) mmHg ($p \leq 0.001$) Vs -18.9 (± 10.68) mmHg ($p \leq 0.001$) while the renal parameters were similar between the two groups. A total of 17 mild drug-related adverse events were reported (TA: 8; TC: 9), with no serious events.

Conclusion: Both the TA and TC FDCs were effective and well tolerated when treating hypertension with renal impairment. The TA FDC may provide better BP reduction with similar reno-protective benefits than the TC FDC.

Keywords: amlodipine, cilnidipine, telmisartan, CCB, renoprotection

Introduction

Hypertension is a complex pathophysiological condition known to cause hypertensive nephropathy or hypertensive nephrosclerosis—progressive renal disorders characterized by structural and functional damage to the kidneys resulting

from chronic, uncontrolled elevation of blood pressure (BP).¹ Hypertension poses a variable risk of renal damage depending on the severity and individual susceptibility.² Hypertension is also significantly associated with increased deaths due to renal failure in India.³ Studies indicate that individuals with hypertension and chronic kidney disease (CKD) experience significantly lower health-related quality of life than the general population, with reduced work productivity and rising healthcare costs further intensifying the disease burden.⁴ A 2024 study evaluating the direct costs of CKD in Asian countries reported the average per patient cost of \$6,344 were spent for renal replacement therapy (RRT) and \$1,500 for non-RRT management in India, highlighting the need for appropriate management of risk factors of CKD, including hypertension.⁵

High BP is a well-established risk factor for kidney dysfunction; it exhibits a linear relationship with CKD incidence and progression. Persistent hypertension damages nephrons, leading to impaired glomerular filtration.⁶ If left untreated, it accelerates CKD progression, eventually advancing to end-stage renal disease; this emphasizes the importance of controlling BP in preventing CKD and its complications.⁷ The renin-angiotensin-aldosterone system (RAAS) contributes to hypertension-related renal dysfunction by increasing glomerular pressure and promoting protein ultrafiltration. Angiotensin II further accelerates renal injury through vasoconstriction, inflammation, and fibrosis. These mechanisms drive the progression of kidney damage in patients with hypertension.⁸

The kidney disease improving global outcomes (KDIGO)-2021 BP guideline recommends a target systolic blood pressure (SBP) of 120 mm/Hg in patients with CKD and recommends the use of 2 or more anti-hypertensive drugs.⁹ While evidence comparing drug combinations in CKD is limited, the KDIGO-2021 and 2020 ISH Global Hypertension Practice Guidelines recommend renin-angiotensin system inhibitors (RASi), angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) as first line therapy.^{9,10} RASi mitigate the RAAS cascade by reducing the synthesis of angiotensin II or blocking its action; this causes vasodilation, decreased aldosterone secretion, and BP reduction.¹¹ If the target BP is not achieved through monotherapy, the 2020 ISH Global Hypertension Practice Guidelines recommend addition of a calcium channel blocker (CCB) or diuretic to RASi.⁹

CCBs such as amlodipine and cilnidipine have demonstrated efficacy in managing hypertension in patients with renal dysfunction, as evidenced by findings from various long-term studies and meta-analyses.^{12–14} CCBs are known to act on the L-type calcium channels in the arteries and heart, which cause the anti-hypertensive effect. Extensive long-term trials have established the major adverse cardiovascular event benefits of amlodipine. It significantly lowers cardiovascular events by preventing counter-regulatory mechanisms, slowing atherosclerosis, providing antioxidant properties, and enhancing nitric oxide production. These findings highlight its potential for enhanced cardiovascular protection. As hypertension management shifts towards combination therapy, amlodipine remains an option for controlling BP and improving cardiovascular outcomes.¹⁵ Cilnidipine, a fourth-generation L/N-type dual CCB, exhibits additional renoprotection by inhibiting sympathetic activity and promoting efferent arteriolar dilation, effectively reducing glomerular hypertension.¹⁶ Although both amlodipine and cilnidipine are recognized for their role in managing hypertension with renal dysfunction, few direct comparative studies are available to guide clinicians in selecting the optimal agent for combination therapy with ARBs. This study aims to address this critical knowledge gap by providing data regarding the efficacy and safety of amlodipine versus cilnidipine in patients with hypertension and renal impairment.

Material and Methods

Trial Design

This open label, randomized, parallel arm, post-marketing trial was conducted at 6 centers across India (namely- Panchsheel Hospital, Delhi; College of Medicine & J.N.M. Hospital, West Bengal; Gillurkar Multispeciality Hospital, Nagpur, Maharashtra; MV Hospital & Research Center, Lucknow, Uttar Pradesh; Udyaan Health Care Pvt. Ltd., Lucknow, Uttar Pradesh; Santosh Hospital, Bengaluru, Karnataka). Participants were randomly assigned in a 1:1 allocation ratio using a computer generated randomization list. The study was performed in accordance with ICH-GCP guidelines and the Declaration of Helsinki. Institutional Ethics Committee approvals were obtained from all study sites before patient enrolment. Written informed consent was obtained from all study participants before enrolment. The trial was registered in the Clinical Trial Registry of India (CTRI No - CTRI/2023/03/051014).

Objectives

The primary objective of this study was to evaluate and compare the effects of the telmisartan-amlodipine fixed-dose combination (FDC) to those of the telmisartan-cilnidipine FDC on renal parameters and BP in patients with hypertension and renal impairment. The secondary objective was to assess and compare the safety profiles of these two treatment regimens within the same patient population.

Participants

Adults aged 18–75 years with hypertension (Systolic Blood Pressure/ diastolic blood pressure [DBP] $\geq 130/80$ mmHg and $< 180/110$ mmHg) and renal impairment (estimated glomerular filtration rate [eGFR] 60–90 mL/min/1.73 m²; urine albumin-creatinine ratio [UACR] 30–600 mg/g) were eligible. Regarding sex distribution, in Group A (telmisartan + amlodipine), there were 42 females and 52 males, while in Group B (telmisartan + cilnidipine), there were 43 females and 51 males. Inclusion required treatment with a two-drug antihypertensive regimen and a stable dose of telmisartan for at least three months prior to enrollment. Additionally, patients must not have received CCB therapy during this period.

Interventions

Eligible subjects were randomized into one of the two treatments groups according to the computer-generated randomization list in 1:1 ratio at baseline (Visit 2), and subjects were allocated to either the Telmisartan plus Amlodipine group or the Telmisartan plus Cilnidipine group. The TA Group received an FDC of telmisartan 40/80 mg and amlodipine 5 mg once daily; the TC Group received an FDC of telmisartan 40/80 mg and cilnidipine 10 mg once daily. Each treatment involved one tablet taken daily, orally with plain water after a meal, for 12 months.

Outcomes

Follow-up visits occurred at 3, 6, 9, and 12 months, with a permissible delay from the last day of window period of 7 days. The primary outcome of the study was comparing the change in UACR from baseline to 12 months between the study groups (measured at baseline, 6 months, and 12 months). The secondary outcome was to compare change in eGFR, serum creatinine levels, and serum uric acid levels (measured at baseline, 6 months, and 12 months), SBP and DBP (measured at baseline, 3 months, 6 months, 9 months, and 12 months) between the study groups.

The incidence of adverse events associated with each treatment combination was compared between the study groups.

Compliance with the study medications, changes in other medications, and adverse events were recorded at each visit. Treatment compliance was monitored by counting the remaining study medication for each participant, with participants required to consume at least 80% of the prescribed doses to be considered compliant.

Concurrent antihypertensive medications, apart from the study medication, were prohibited. Other concomitant medications were allowed at the investigator's discretion, except those contraindicated as per the prescribing information.

Sample Size Calculation

Existing data suggest that the difference in UACR between cilnidipine and amlodipine at 12 months from baseline is 0.001 mg/g, with a common standard deviation of 10. (17) Based on these findings, the estimated effect size for the telmisartan-amlodipine FDC versus the telmisartan-cilnidipine FDC was assumed to be 0.5 mg/g. To achieve 90% power with a two-sided significance level of 5% and at a non-inferiority margin of 10%, 85 participants per treatment arm were required. Accounting for a 10% drop-out rate and other protocol deviations, a total of 94 participants per treatment group (188 in total) were required to be enrolled in this study.

Statistical Analysis

All analyses were performed using R Software. The Safety Set (SAF) comprised all participants who received at least one dose of the study drug and was used for all safety analyses. The Full Analysis Set (FAS) included all enrolled participants who received at least one dose of the study drug and had at least one post-baseline efficacy assessment. The Per-Protocol Set (PPS) consisted of all participants in the FAS who had no major protocol deviations. The major protocol

deviations were predefined in the statistical analysis plan before database lock. Subgroup analysis was also performed for participants with diabetes. Missing efficacy data were imputed using the Last Observation Carried Forward method. Data were summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints. P-values for continuous variables were computed using the Kruskal–Wallis test, while within-group p-values were determined using on the Wilcoxon signed-rank test.

Results

Participant Flow

Of the 228 patients screened, 188 were found to be eligible and randomly assigned to the TA Group (94 participants) or the TC Group (94 participants). Seven participants were lost to follow-up before study completion. The FAS included 185 participants, while the SAF comprised all 188 randomized participants. A total of 181 participants completed the study and were included in the PPS (Figure 1).

Baseline characteristics, including age, sex, body mass index (BMI), SBP, DBP, serum creatinine, UACR, and other relevant parameters were well matched between the two groups, as presented in Tables 1 and 2.

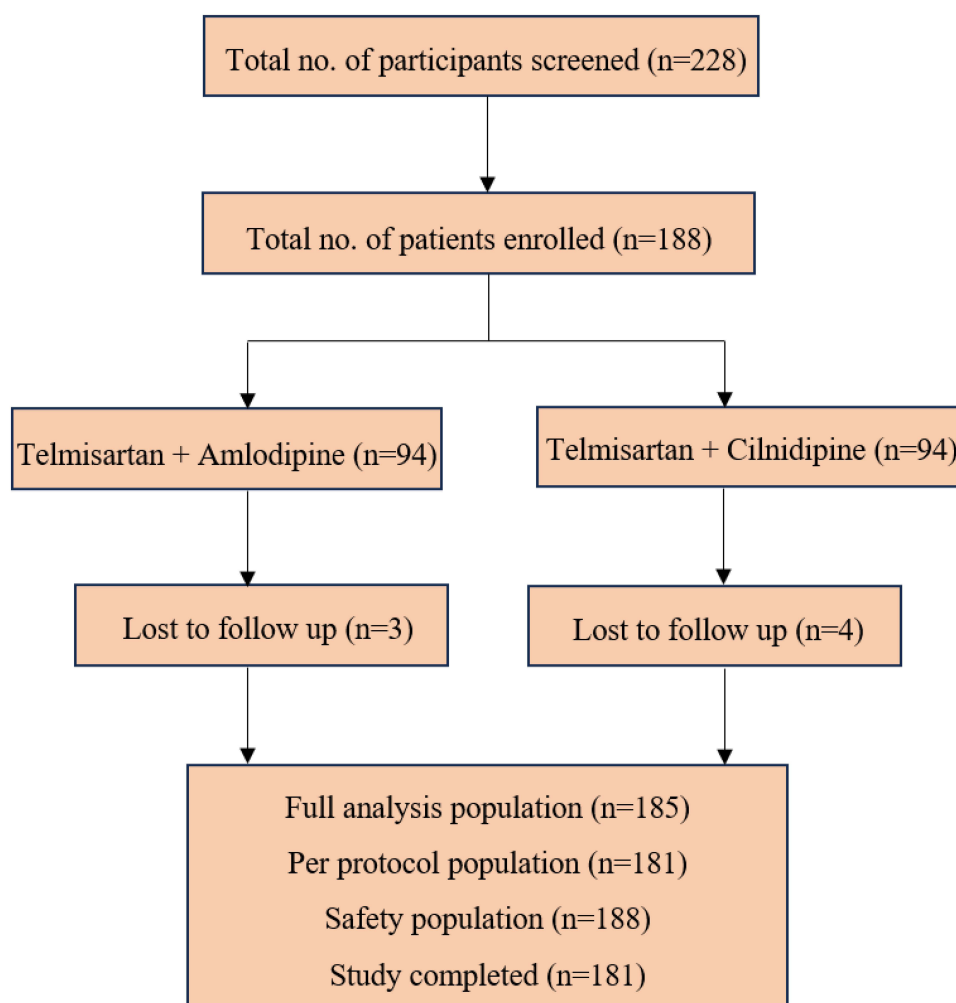


Figure 1 Consort flow chart.

Table 1 Baseline Characteristics Of The Patients

Statistic Summary	FDC of Telmisartan 40/80 mg + Amlodipine 5 mg (N=94)	FDC of Telmisartan 40/80 mg + Cilnidipine 10 mg (N=94)	P-Value
Sex n (%)			0.8835
Female	42 (44.7)	43 (45.7)	
Male	52 (55.3)	51 (54.3)	
Age (years)			0.1583
Mean $\pm$ SD	52.5 $\pm$ 10.85	54.7 $\pm$ 10.36	
Height (cm)			0.6495
Mean $\pm$ SD	159.7 $\pm$ 7.72	159.2 $\pm$ 9.55	
Weight (kg)			0.6587
Mean $\pm$ SD	68.9 $\pm$ 10.24	68.3 $\pm$ 10.92	
BMI (kg/m ²)			0.9228
Mean $\pm$ SD	27.1 $\pm$ 4.07	27.1 $\pm$ 5.13	
Systolic blood pressure (mmHg)			0.3637
Mean $\pm$ SD	151.2 $\pm$ 10.93	149.7 $\pm$ 11.33	
Diastolic blood pressure (mmHg)			0.7196
Mean $\pm$ SD	89.1 $\pm$ 5.21	88.9 $\pm$ 4.49	

Notes: p-values are computed using the Kruskal–Wallis Test for continuous variables.

Abbreviations: BMI, body mass index; SD, standard deviation.

Table 2 Summary And Statistical Analysis Of Renal Parameters

Renal parameter	Visit	Telmisartan + Amlodipine FDC (Mean $\pm$ SD) (N = 91)	Change from Baseline (Mean $\pm$ SD)	P Value (Within Group)	Telmisartan + Cilnidipine FDC (Mean $\pm$ SD) (N = 90)	Change from Baseline (Mean $\pm$ SD)	P Value (Within-Group)	P-Value Between Groups
Urinary albumin-creatinine ratio (UACR) (mg/g)	Baseline	183.3 $\pm$ 144.02	NA	NA	143.8 $\pm$ 120.16	NA	NA	0.1031
	6 Months	96.15 $\pm$ 107.7	-87.2 $\pm$ 152.3	<0.0001	81.19 $\pm$ 86.59	-62.6 $\pm$ 123.3	<0.0001	0.1330
	12 months	64.33 $\pm$ 102.6	-119 $\pm$ 157.7	<0.0001	46.28 $\pm$ 57.51	-97.5 $\pm$ 128.6	<0.0001	0.2401
Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²)	Baseline	75.0 $\pm$ 8.80	NA	NA	75.1 $\pm$ 8.62	NA	NA	0.8547
	6 months	87.10 $\pm$ 18.72	12.09 $\pm$ 18.08	<0.0001	85.07 $\pm$ 17.27	+9.97 $\pm$ 17.84	<0.0001	0.5946
	12 months	94.54 $\pm$ 16.96	+19.53 $\pm$ 19.44	<0.0001	95.98 $\pm$ 20.53	+20.88 $\pm$ 21.26	<0.0001	0.9842

(Continued)

Table 2 (Continued).

Renal parameter	Visit	Telmisartan + Amlodipine FDC (Mean $\pm$ SD) (N = 91)	Change from Baseline (Mean $\pm$ SD)	P Value (Within Group)	Telmisartan + Cilnidipine FDC (Mean $\pm$ SD) (N = 90)	Change from Baseline (Mean $\pm$ SD)	P Value (Within-Group)	P-Value Between Groups
Serum creatinine level (mg/dL)	Baseline	1.04 $\pm$ 0.22	NA	NA	1.0 $\pm$ 0.20	NA	NA	0.6686
	6 months	0.98 $\pm$ 0.34	-0.06 $\pm$ 0.28	<0.0001	0.96 $\pm$ 0.20	-0.05 $\pm$ 0.22	<0.0001	0.5522
	12 months	0.97 $\pm$ 1.00	-0.07 $\pm$ 0.91	<0.0001	0.92 $\pm$ 0.56	-0.09 $\pm$ 0.60	<0.0001	0.6539
Serum uric acid level (mg/dL)	Baseline	5.4 $\pm$ 1.68	NA	NA	5.2 $\pm$ 1.56	NA	NA	0.2758
	6 months	5.37 $\pm$ 1.08	-0.01 $\pm$ 1.47	0.8998	5.09 $\pm$ 1.38	-0.06 $\pm$ 1.73	0.7545	0.7506
	12 months	5.17 $\pm$ 1.21	-0.21 $\pm$ 2.00	0.3758	5.01 $\pm$ 1.14	0.14 $\pm$ 1.90	0.7057	0.7303

Notes: Between-group p-values are determined using the Kruskal–Wallis Test; Within-group p-values are determined using the Wilcoxon signed-rank test.

Abbreviations: FDC, fixed dose combination; SD, standard deviation; UACR, urinary albumin creatinine ratio.

Effectiveness Evaluation

At both 6 and 12 months, statistically significant improvements were observed in the UACR, eGFR, and serum creatinine levels in both groups compared to baseline ($p < 0.0001$). However, reductions in serum uric acid level were not statistically significant compared to baseline and between groups. The changes in renal parameters at 12 months were comparable between groups.

Both the TA and TC groups demonstrated a statistically significant reduction in SBP and DBP from baseline across all time points, indicating effective BP control throughout the study period. Notably, at 9 and 12 months, the TA group achieved a greater reduction in SBP than the TC group, with a decrease of 20.74 mmHg versus 16.9 mmHg ($p = 0.0430$) at 9 months and 25.4 mmHg versus 20.6 mmHg ($p = 0.0397$) at 12 months, respectively (Figure 2a). The DBP reductions were comparable between both groups at all time points (Figure 2b).

In the diabetes subpopulation, both groups exhibited statistically significant reductions in UACR and improvements in eGFR at 12 months. Serum creatinine and uric acid levels remained stable throughout the study in both groups (Table 3).

In the diabetes subpopulation, both groups demonstrated statistically significant reductions in SBP and DBP at all follow-up visits. At 12 months, the reduction in SBP was significantly greater in the TA Group ($p = 0.0487$), (Figure 3a) while changes in DBP were similar between the groups (Figure 3b).

Safety Evaluation

A total of 60 participants (31.9%) experienced 79 adverse events (Table 4). The details of adverse events are further reported according to system-organ classification. A total of 17 (8%) drug-related treatment-emergent adverse events were reported in 15 participants. All the participants with adverse events recovered fully.

No serious adverse events reported during the study duration.

Discussion

The study demonstrated that both FDCs led to significant improvements in renal parameters (UACR, eGFR, and serum creatinine) and BP (SBP and DBP) over the 12-month study period. The renoprotective effect seen in the TA group was comparable to that seen in the TC group, while the TA group showed superior SBP reduction at 9 and 12 months. Both treatments were well-tolerated, with a good safety profile.

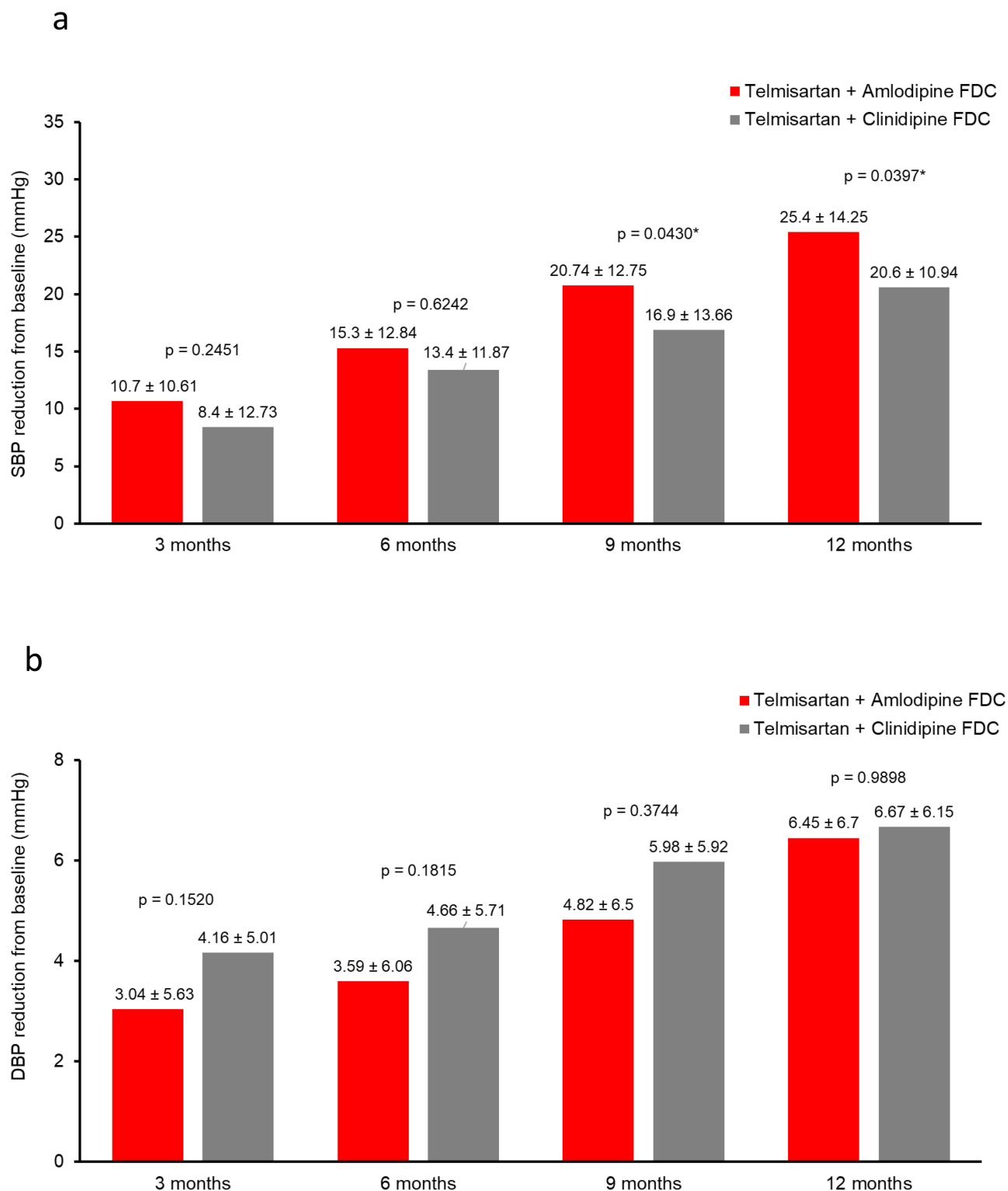


Figure 2 Comparison of systolic and diastolic blood pressure between groups. (a) Comparison of systolic blood pressure (SBP) levels between groups. (b) Comparison of diastolic blood pressure (DBP) levels between groups. *P value is significant ($p < 0.05$). Between-group p-values are determined using the Kruskal–Wallis test.

Table 3 Summary And Statistical Analysis Of Renal Parameters In The Sub-Population With Diabetes

Renal Parameter	Visit	Telmisartan + Amlodipine FDC (Mean $\pm$ SD)	Change from Baseline (Mean $\pm$ SD)	P-Value (Within- Group)	Telmisartan + Cilnidipinefdc (Mean $\pm$ SD)	Change from Baseline (Mean $\pm$ SD)	P Value (Within- Group)	P Value (Between- Group)
Urinary albumin- creatinine ratio (UACR) (mg/g)	Baseline	117.2 $\pm$ 104.9	NA	NA	103.6 $\pm$ 80.85	NA	NA	0.6701
	6 Months	94.18 $\pm$ 144.7	-23.0 $\pm$ 153.7	0.1186	86.16 $\pm$ 105.2	-17.4 $\pm$ 97.84	0.0136	0.8313
	12 months	62.99 $\pm$ 123.4	-54.2 $\pm$ 138.4	<0.0001	47.38 $\pm$ 68.09	-56.2 $\pm$ 91.64	<0.0001	0.8401
Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m ²)	Baseline	77.10 $\pm$ 9.34	NA	NA	77.30 $\pm$ 8.97	NA	NA	0.7575
	6 months	86.13 $\pm$ 15.74	9.03 $\pm$ 15.38	0.0013	80.43 $\pm$ 16.76	+3.12 $\pm$ 17.15	0.0764	0.1592
	12 months	88.41 $\pm$ 18.95	+11.31 $\pm$ 21.78	0.0018	96.68 $\pm$ 23.40	+19.38 $\pm$ 24.74	<0.0001	0.3910
Serum creatinine level (mg/dL)	Baseline	1.00 $\pm$ 0.25	NA	NA	0.96 $\pm$ 0.22	NA	NA	0.6164
	6 months	0.99 $\pm$ 0.19	-0.00 $\pm$ 0.19	0.4814	1.00 $\pm$ 0.23	0.04 $\pm$ 0.22	0.2376	0.2411
	12 months	0.96 $\pm$ 0.36	-0.04 $\pm$ 0.27	0.0665	0.99 $\pm$ 0.80	0.03 $\pm$ 0.84	0.0755	0.8929
Serum uric acid level (mg/dL)	Baseline	5.15 $\pm$ 1.49	NA	NA	5.10 $\pm$ 1.61	NA	NA	0.5153
	6 months	5.13 $\pm$ 1.07	-0.02 $\pm$ 1.23	0.9118	5.07 $\pm$ 1.80	-0.03 $\pm$ 1.94	0.7991	0.9508
	12 months	5.53 $\pm$ 1.60	0.38 $\pm$ 1.97	0.4984	4.99 $\pm$ 1.35	-0.11 $\pm$ 2.20	0.7893	0.7155

Notes: SD, standard deviation Between-group p-values are determined using the Kruskal–Wallis Test. Within-group p-values are determined using the Wilcoxon signed-rank test.

Abbreviations: SD, Standard Deviation; eGFR, estimated glomerular filtration rate; FDC, fixed dose combination.

UACR is a well-established and reliable biomarker for assessing renal damage in hypertensive nephropathy.¹⁷ The strong correlation of UACR with disease progression and its prognostic value in predicting renal and cardiovascular outcomes makes it an ideal choice as the primary endpoint for this study.¹⁸ Telmisartan effectively manages hypertension and renal impairment, as evidenced by significant reductions in the UACR in clinical studies. In a retrospective cohort study of 1095 patients with hypertension in India, treatment with telmisartan monotherapy for an average duration of 278 days resulted in a significant reduction in UACR, decreasing from 113.58 mg/g at baseline to 77.29 mg/g at follow-up ($p=0.0012$).¹⁹ A meta-analysis by Cheng et al compared the renoprotective effects of RAAS plus CCB to those of RAAS plus diuretic therapy. The analysis demonstrated that RAAS plus CCB was superior in preserving eGFR/CrCl and lowering serum creatinine levels.²⁰ Given that these parameters serve as key markers of kidney function, particularly in early-stage renal disease, these findings suggest a potential advantage of RAAS plus CCB in mitigating renal decline.^{21,22} Given the established renoprotective benefits of RASi, the SAKURA trial also highlights the potential of combining them with CCBs to further improve renal outcomes.²³

The findings of this trial align with the results from the SAKURA trial. This was a prospective, multicenter, open-label, randomized study in 367 patients comparing the antialbuminuric effects of L-/N-type and L-type CCBs in patients with hypertension, diabetes, and microalbuminuria treated with RASi. The UACR values decreased by 3.57 mg/g and 0.78 mg/g for the cilnidipine and amlodipine groups after treatment, respectively ($p=0.224$). Similarly, the serum Cr, and eGFR changes were comparable between the study groups.²³ Amlodipine demonstrated renoprotective effects comparable to those of cilnidipine, supporting its role in patients receiving RASi therapy.

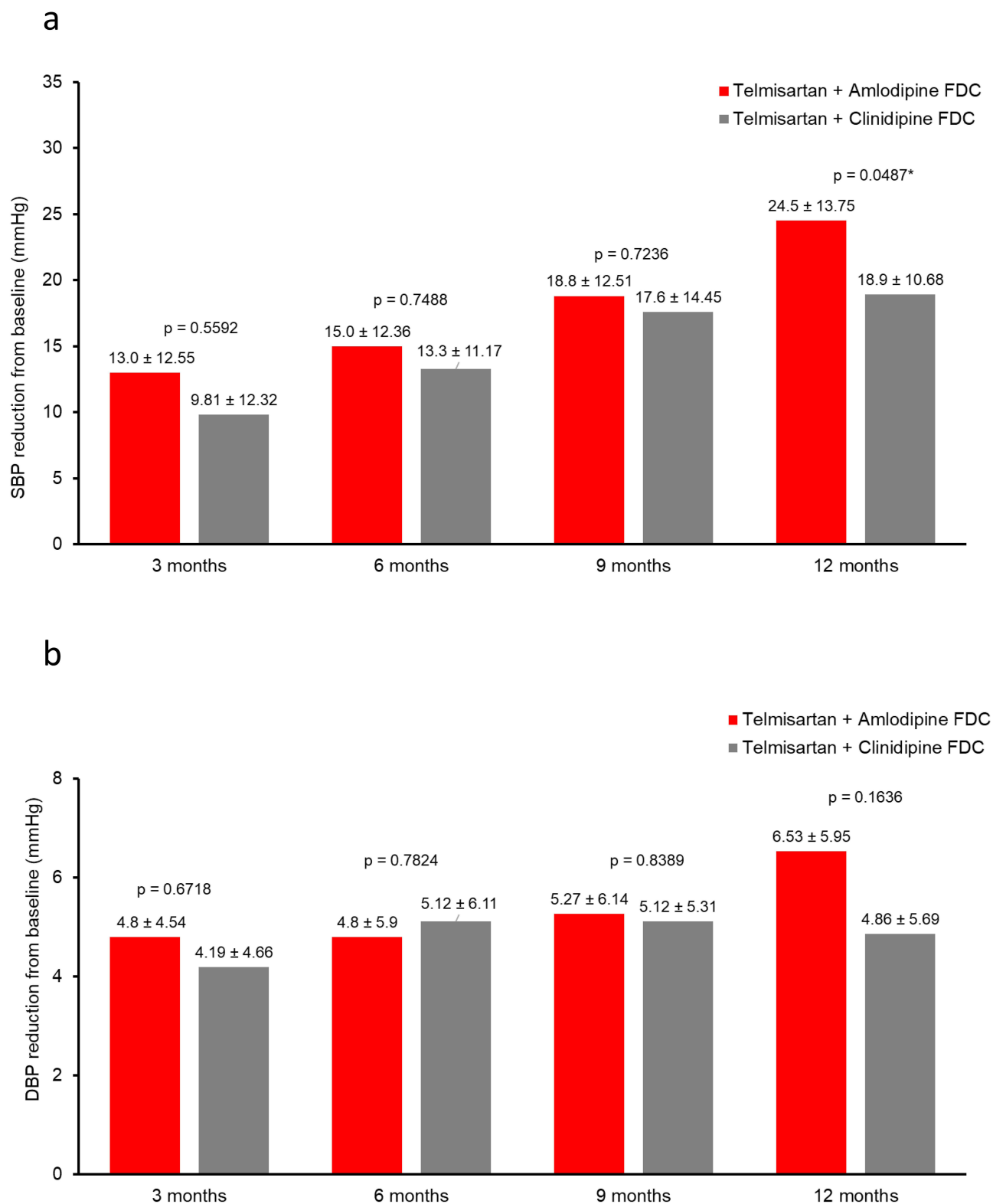


Figure 3 Comparison of systolic and diastolic blood pressure in the diabetic sub-population. (a) Comparison of systolic blood pressure (SBP) levels in the diabetic sub-population. (b) Comparison of diastolic blood pressure (DBP) levels in the diabetic sub-population. *P value is significant ($p < 0.05$). Between-group p-values are determined using the Kruskal–Wallis test.

Table 4 Drug-Related Adverse Events

AE term	TA Group (N = 94) n(%) E	TC Group (N = 94) n(%) E
Any TEAEs	33 (35.1%) 44	27 (28.7) 35
Drug-related TEAEs	8 (8.5%) 8	7 (7.44%) 9
Serious TEAEs	0	0
Pedal edema	3 (3.1)	1 (1.1)
Urinary tract infection	1 (1.1)	0
Meniere disease	1 (1.1)	0
Abdominal pain	1 (1.1)	0
Dizziness/ vertigo/ weakness	1 (1.1)	3 (3.1)
Headache	1 (1.1)	0
Shortness of breath	0	1 (1.1)
Hypotension	0	1 (1.1)
High random blood sugar level	0	1 (1.1)
Fever	0	2 (2.1)

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; N, number of subjects; E, number of events.

Monotherapy studies of amlodipine versus cilnidipine have reported greater renoprotective benefits with cilnidipine. Some studies have reported contrasting findings as well. Kojima et al found that cilnidipine associated with a smaller decline or more stable eGFR than amlodipine when used as monotherapy in patients with hypertension and renal disease, suggesting superior renal protection, despite both drugs achieving comparable BP control. However, the study had several limitations, including a small sample size, unmatched baseline characteristics, and the effect of other antihypertensive medications not accounted for in the statistical analysis.²⁴ Similarly, Fujita et al reported that cilnidipine demonstrated greater renal benefits by lowering the urinary protein-to-creatinine ratio to a greater extent compared to amlodipine as monotherapy, while both drugs maintained effective BP control in patients with hypertension and kidney disease.²⁵ However, findings from our study suggest that amlodipine demonstrates renoprotective effects comparable to those of cilnidipine when combined with RASi therapy.

SBP and DBP are widely and clinically recognized predictors of nephropathy, serving as critical markers for assessing the risk and progression of kidney damage.²⁶ Among these, SBP has been shown to be a stronger predictor of renal outcomes than DBP, particularly in patients with nephropathy secondary to type 2 diabetes. Therefore, comparison of SBP between treatment groups is essential to evaluate its impact on renal outcomes and to assess the therapeutic effectiveness of interventions aimed at mitigating kidney damage.²⁷ In our study, both treatment groups demonstrated significant reductions in SBP and DBP over 12 months. The TA Group achieved a greater reduction in SBP at 12 months than the TC Group (-24.5 mmHg vs. -18.9 mmHg; $p = 0.0487$). A previous study by Ando et al (SAKURA study), also showed that both cilnidipine (SBP and DBP, after treatment: $130.40 \pm 13.93/73.37 \pm 10.20$ mmHg) and amlodipine ($129.65 \pm 13.33/71.75 \pm 9.79$ mmHg) decreased the BP equally and significantly; moreover, the changes were comparable between the groups (SBP and DBP: $P = 0.88$ and $P = 0.51$, respectively).²³ Similarly, Fujita et al reported that both cilnidipine (SBP/DBP: $133.1 \pm 15.6/75.6 \pm 8.7$ mmHg) and amlodipine ($134.5 \pm 16.6/77.9 \pm 9.4$ mmHg) significantly reduced BP over one year, with no significant differences between the groups (SBP: $P = \text{NS}$, DBP: $P = \text{NS}$).²⁵

The safety profile was comparable between the two groups, with 31.9% of the participants experiencing mild-to-moderate adverse events, including fever, headache, and body pain; no serious adverse events were reported. The adverse events reported in this study are known adverse events when treating with amlodipine and cilnidipine; no unknown

adverse events were found.^{28,29} Pedal edema was reported in fewer patients and was not a significant concern in this study. All adverse events were resolved by the end of the study.

The study has a few limitations, including its open-label design and the need for a longer follow-up period, as both hypertension and CKD are chronic conditions requiring extended observation. Despite this, the findings suggest that amlodipine and cilnidipine provide comparable renoprotection with a greater SBP reduction with amlodipine. Both drugs exhibited similar safety profiles, but further studies with larger sample sizes and extended follow-up durations are warranted to validate these findings and gain deeper insights into the long-term effectiveness and safety of these treatment regimens.

Conclusion

Our study compared the effectiveness and safety of a telmisartan-amlodipine FDC versus a telmisartan-cilnidipine FDC in a post-marketing setting among Indian patients. It offers a comprehensive assessment of the profiles of these two FDCs based on objective parameters. The use of objective markers such as UACR, eGFR, and BP provides reliable measures of renal outcomes. Additionally, the study followed patients over a 12-month period, offering long-term data on effectiveness and safety, although it may not provide insights into long-term renal and cardiovascular outcomes.

In conclusion, telmisartan-amlodipine FDC and telmisartan-cilnidipine FDC both demonstrated comparable renoprotection, antihypertensive effect, and safety. The telmisartan-amlodipine FDC showed a greater SBP reduction and can be considered optimal for managing Indian patients with hypertension and renal impairment.

Data Sharing Statement

The data set generated and/or analyzed during the current study are available from the corresponding author on reasonable request and subject to institutional data sharing agreement. All data shared will be de-identified to protect participant confidentiality.

Acknowledgments

We would like to extend our thanks to all the institutes and respective investigators and team members for their support. We also appreciate the CRO support by IR Innovate Research Pvt. Ltd., India for end to end clinical trial management. We also thank Ms Rujuta Gadkari & Kiransing Pawar (Glenmark Pharmaceuticals) for their project management support in the study. We acknowledge the support of VeritasQ for manuscript development support.

Funding

This study was funded by Glenmark Pharmaceuticals Limited. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

Dr Mayur Jadhav, Dr Sanjay Y Choudhary, Dr Saiprasad Patil, Dr Sumit Bhushan, Dr Divakar A and Dr Hanmant Barkate are employees of Glenmark pharmaceuticals limited. All other authors have no conflicts of interest that are directly relevant to the content of this article.

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