Efficacy and safety of a novel low-dose triple single-pill combination of telmisartan, amlodipine and indapamide, compared with dual combinations for treatment of hypertension: a randomised, double-blind, active-controlled, international clinical trial

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Abstract

Background: Single-pill combinations (SPCs) of three low-dose antihypertensive drugs can improve hypertension control but are not widely available. A key issue for any combination product is the contribution of each component to efficacy and tolerability. This trial compared a new triple SPC called GMRx2, containing telmisartan, amlodipine, and indapamide, with dual combinations of components for efficacy and safety.

Methods: In this international, randomised, double-blind, active-controlled trial, we enrolled adults with hypertension receiving between zero and three antihypertensive drugs, with a screening systolic blood pressure (SBP) ranging from 140-179 mm Hg (on no drugs) to 110-150 mm Hg (on three drugs). Participants were recruited from Australia, the Czech Republic, New Zealand, Poland, Sri Lanka, the UK, and the USA. In a 4-week active run-in, existing medications were switched to GMRx2 half dose (telmisartan 20 mg, amlodipine 2·5 mg, and indapamide 1·25 mg). Participants were then randomly allocated (2:1:1:1) to continued GMRx2 half dose or to each possible dual combination of components at half doses (telmisartan 20 mg with amlodipine 2·5 mg, telmisartan 20 mg with indapamide 1·25 mg, or amlodipine 2·5 mg with indapamide 1·25 mg). At week 6, doses were doubled in all groups, unless there was a clinical contraindication. The primary efficacy outcome was mean change in home SBP from baseline to week 12, and the primary safety outcome was withdrawal of treatment due to an adverse event from baseline to week 12. Secondary efficacy outcomes included differences in clinic and home blood pressure levels and control rates. This study is registered with ClinicalTrials.gov, NCT04518293, and is completed.

Findings: The trial was conducted between July 9, 2021 and Sept 1, 2023. We randomly allocated 1385 participants to four groups: 551 to GMRx2, 276 to telmisartan-indapamide, 282 to telmisartan-amlodipine, and 276 to amlodipine-indapamide groups. The mean age was 59 years (SD 11), 712 (51%) participants self-reported as female and 673 (48·6%) male, and the mean clinic

blood pressure at the screening visit was 142/85 mm Hg when taking an average of 1·6 blood pressure medications. Following the run-in on GMRx2 half dose, the mean clinic blood pressure level at randomisation was 133/81 mm Hg and the mean home blood pressure level was 129/78 mm Hg. At week 12, the mean home SBP was 126 mm Hg in the GMRx2 group, which was lower than for each of the dual combinations: -2·5 (95% CI -3·7 to -1·3, p<0·0001) versus telmisartan-indapamide, -5·4 (-6·8 to -4·1, p<0·0001) versus telmisartan-amlodipine, and -4·4 (-5·8 to -3·1, p<0·0001) versus amlodipine-indapamide. For the same comparisons, differences in clinic blood pressure at week 12 were 4·3/3·5 mm Hg, 5·6/3·7 mm Hg, and 6·3/4·5 mm Hg (all p<0·001). Clinic blood pressure control rate below 140/90 mm Hg at week 12 was superior with GMRx2 (74%) to with each dual combination (range 53-61%). Withdrawal of treatment due to adverse events occurred in 11 (2%) participants in the GMRx2 group, four (1%) in telmisartan-indapamide, three (1%) in telmisartan-amlodipine, and four (1%) in amlodipine-indapamide, with none of the differences being statistically significant.

Interpretation: A novel low-dose SPC product of telmisartan, amlodipine, and indapamide provided clinically meaningful improvements in blood pressure reduction compared with dual combinations and was well tolerated. This SPC provides a new therapeutic option for the management of hypertension and its use could result in a substantial improvement in blood pressure control in clinical practice.