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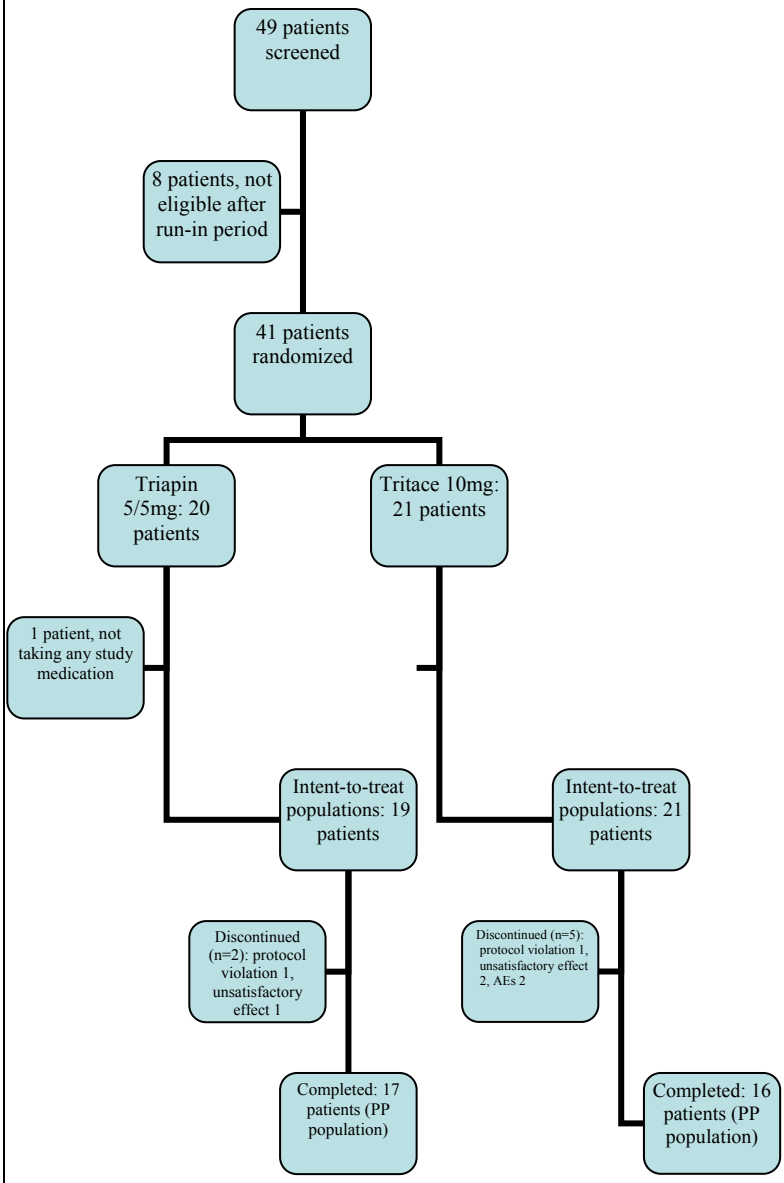
Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00841880
		Study Code:	RAMFE_L_03420
Generic drug name:	Ramipril + Felodipine	**Date:**	24 August 2010

Title of the study:	A Prospective, Open Label, Randomized, Comparative Study of Ramipril 5mg plus Felodipine 5mg Combined Regimen and Ramipril 10mg in Uncontrolled Hypertensive Patients		
Investigator(s):	PI: Dr. Chung-Hsiang Liu Department of Internal Medicine China Medical University Hospital Taichung, Taiwan		
Study center(s):	China Medical University Hospital		
Publications (reference):	1. Clin Exp Hyperts 1999; 21: 1447-1462. 2. Br J Pharmac 1993; 36: 323-330. 3. Int J Clin Pract 2006; 60(3): 265-274.		
Study period: Date first **patient/subject** enrolled: 21-Jan-2009 Date last **patient/subject** completed: 07-Sep-2009		**Phase of development:** IV	
Objectives:	Primary Objective ➢ To compare the reduction in SBP following a 8-week regimen of ramipril 5mg plus felodipine 5mg versus ramipril 10mg Secondary Objectives ➢ To compare the response rate (defined as office seated SBP/DBP reduction of more than 10mmHg from baseline), and BP controlled rate on SBP or DBP or both (defined as SBP < 140 mmHg and / or DBP < 90 mmHg, and as SBP < 130 mmHg and / or DBP < 80 mmHg in diabetes, chronic kidney disease, known CAD or CAD equivalent, or 10-year Framingham risk score > 10%). ➢ To ascertain the safety and tolerability of ramipril/ felodipine versus ramipril in Taiwanese population. To compare compliance with fixed dose combination of ramipril/felodipine versus ramipril treatment.		
Methodology:	A prospective, open-label, randomized, active-controlled, parallel group study		
Number of subjects:	Planned: 60 (49 subjects were screened)	Randomized: 41	Treated: 40
Evaluated:	Efficacy: 40	Safety: 40	

49 patients were enrolled into a 2-week run-in phase with ramipril 5mg treatment. After run-in period, 41 patients met the entry criteria and were randomly allocated to receive Triapin® 5/5mg (N=20) or Tritace® 10mg (N=21). One patient in Triapin® group, not taking any study medication, was excluded from ITT population . 7 subjects (2 in Triapin® group, 5 in the Tritace® group) from ITT populations were excluded from the PP population due to protocol violations or early withdrawals.



Diagnosis and criteria for inclusion:	Inclusion criteria: • Male or female outpatients aged > 20 years • Uncontrolled essential hypertension defined by office SBP/DBP > 140/90 or > 130/80 mmHg with co morbidities or risk factors (diabetes mellitus, chronic kidney disease, known CAD, CAD equivalent or 10-year Framingham risk score > 10%) • Patients must be previously untreated or treated only with a single antihypertensive therapy at usual dose for at least 4 weeks • Patient or legally acceptable representative have signed the written informed consent form Exclusion criteria: • Females: who are pregnant or breast feeding or of childbearing age without an effective contraception • Office diastolic BP > 110 mmHg or office systolic BP > 180 mmHg • Hypersensitivity to ramipril, felodipine or to any of the excipients • Bilateral stenosis of the renal arteries, or unilateral stenosis in the single kidney • History of intolerance to any ACE inhibitor • History of significant renal diseases including: serum creatinine > 3.0 mg/dl, or creatinine clearance < 30 ml/min. • History of hereditary and/or idiopathic angioedema; or angioedema associated with previous ACEI. • Significant cardiovascular disease, multiple drug allergies, bronchospastic disease or other malignancies requiring current medication • Hepatic disease as indicated by any of the following : ALT or AST > 3 x upper limit of normal, or serum bilirubin > 2 x upper limit of normal • Any other condition or therapy that, in the investigator's opinion, or as indicated in the product(s) label, may pose a risk to the patient or interfere with the study objective • Any other investigational drug given within 30 days of initiation of therapy, and participation in other clinical studies while enrolled in this protocol.	
Investigational product: Dose: Administration:	Triapin ® 5/5 mg 1 tablet per day, which contains 5 mg felodipine and 5 mg ramipril per tab Orally	
Duration of treatment: 8 weeks		**Duration of observation:** 8 weeks

Reference therapy: Dose: Administration:	Ramipril (Tritace®) 10mg qd orally
Criteria for evaluation: **Efficacy**	Primary: ➢ The change in mean SBP (△ SBP) at office between the initial state (at visit 2, randomization) and at the end of the study (at visit 4, week 8). (△ SBP = SBP w0 – SBP w8) Secondary: ➢ Office DBP measurement at baseline and after 8-week treatment ➢ Office SBP and DBP measurements after 4-week treatment ➢ Percentage of responders after 4 and 8-week of treatment – Responders: defined as SBP/DBP reduced > 10mmHg from baseline (at visit 2) ➢ Percentage of normalized patients after 4 and 8-week of treatment – normalized : defined as mean sitting BP < 140/90 mmHg, and as < 130/80 mmHg in patients with compelling indications (DM, CKD, CAD pts or 10-yrs Framingham risk score > 10%) ➢ Compliance was assessed using pill count at week 8
Safety:	The criteria for evaluation of safety include treatment-emergent reported or observed adverse events and laboratory tests.
Statistical methods:	■ Demography and baseline characteristics: descriptive statistics were used for continuous variables and frequency tables were provided for categorical data. ■ All efficacy analyses were performed on an intent-to-treat (ITT) basis, defined as subjects who received at least one dose of a randomized study drug and had baseline assessment. ■ Primary efficacy endpoint: mean change in office BP from randomization to week 8 was compared between the two treatment groups using Wilcoxon Rank-Sum Test. ■ Secondary efficacy endpoints: Continuous variables were compared by Wilcoxon Rank-Sum Test, category variables were compared by Fisher's Exact Test. ■ P values were 2-tailed and considered significantly if $p < 0.05$.

Summary of efficacy results:	➢ Patients with uncontrolled hypertension were randomized to receive either Triapin 5/5mg (n=20) or Tritace 10mg (n=21) over an 8 week treatment period. All demographic and clinical characteristics were well balanced between groups. At randomization, mean sitting SBP/DBP were 146.5/92.1 mmHg in Triapin group and 146.8/90.9 mmHg in Tritace group. ➢ Primary endpoint assessment showed a similar SBP reduction with Triapin (-9.6 ± 14.33 mmHg) as compared with Tritace (-2.3 ± 12.15 mmHg) at week 8 (p=0.146). ➢ ITT analysis found that the decrease in mean DBP was significantly greater with Triapin group compared with Tritace group (-4.3 ± 7.76 vs 0.8 ± 8.88 mmHg; p=0.038) ➢ After 4 weeks of treatment, decreases in SBP/DBP were noted in both treatment groups. However, a statistically significant decrease from baseline was achieved only by Triapin (p <0.05) after 8 weeks of treatment. ➢ Higher percentage of the patients in Triapin group were classified as responders (47% vs 19% in Tritace group, p=0.091). At week 8, 66.7% of patients treated by Triapin and 52.9% in the Tritace group had normalized SBP; while the proportion of patients achieved DBP normalization were 61.1% and 41.2% in Triapin and Tritace group respectively. ➢ Treatment compliance rates were similar in each treatment arm (95.1± 17.57% vs 84.7 ± 25.03 %; Triapin vs Tritace, p=0.079)
Safety results:	There were 34 TEAEs reported, 13 in Triapin group and 21 in Tritace group. Majority of the TEAEs reported were mild to moderate in degree. Drug-related AEs from the study occurred more frequently in Tritace group (Triapin vs Tritace: 20% vs 38%, p= 0.306). This higher incidence of drug-related AEs in Tritace group was due to higher incidence of cough, compared with Triapin group. No SAE was reported during the study period.
Date of report:	02-Feb-2009