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Sponsor/company:	Bristol-Myers Squibb and Sanofi-Aventis	**ClinialTrials.gov Identifier:**	NCT00562809
		Study Code:	L_8829
Generic drug name:	Irbesartan	**Date:**	26 Nov 2007

Title of the study:	The Efficacy and Safety of Avalide® 150/12.5 mg and Avalide® 300/25 mg in Patients with Hypertension Uncontrolled on Monotherapy	
Investigator(s):	119 (125 projected)	
Study center(s):	119 (125 projected)	
Publications (reference):	None	
Study period: Date first patient enrolled: 25 July 2003 Date last patient completed: 17 August 2004		**Phase of development:** IV
Objectives:	The primary objective of the study was to quantify the reduction in systolic blood pressure (SBP) fromAvalide 300/25 mg. The secondary objectives of the study were to: >Quantify the reduction in diastolic blood pressure (DBP) from Avalide 300/25 mg. >Quantify the reductions in SBP and DBP from Avalide 150/12.5 mg. >Quantify SBP and DBP response rates and control rates from Avalide 150/12.5 mg and Avalide 300/25 mg. >Achieve the primary and the secondary objectives listed above for each of various subgroups defined by age, gender, race/ethnicity, metabolic syndrome status, type 2 diabetes mellitus (T2DM) status and previous antihypertensive therapy. >Assess the safety of Avalide 150/12.5 mg and Avalide 300/25 mg, respectively. >Quantify changes in high-sensitivity C-reactive protein (hs-CRP; added by the Statistical Analysis Plan, dated 01 September 2004).	

Methodology:

This was a multicenter, prospective, open-label, single-arm study designed to demonstrate the efficacy and safety of Avalide at a low dose (150/12.5 mg) and at a high dose (300/25 mg) in patients with mild to moderate hypertension and uncontrolled SBP (140–159 mmHg for patients without T2DM; or 130–159 mmHg for patients with T2DM) on monotherapy. Following screening and a 4- to 5-week placebo run-in period, patients received once-daily administration of hydrochlorothiazide (HCTZ) 12.5 mg for 2 weeks. This was followed by once-daily administration of Avalide 150/12.5 mg for 8 weeks and progression to Avalide 300/25 mg once-daily for a further 8 weeks. Progression to each phase of the study was dependent upon meeting the following blood pressure (BP) qualification criteria:

BP qualification criteria at the start of each study phase

	Patients without diabetes		Patients with diabetes	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Screening	140–159	70–109	130–159	70–109
Placebo run-in	140–179	70–109	130–179	70–109
HCTZ 12.5 mg	140–179	70–109	130–179	70–109
Avalide 150/12.5 mg	140–179	70–109	130–179	70–109
Avalide 300/25 mg	120–179	70–109	120–179	70–109

Number of patients:	Planned: 1042	Randomized: 1005
Diagnosis and criteria for inclusion:	Consenting male and female patients of 18 years or older who had hypertension with uncontrolled SBP on monotherapy for at least 4 weeks were included in the study. Monotherapy was defined as treatment with one antihypertensive medication. A fixed combination therapy of HCTZ and triamterene was considered monotherapy (Amendment 3). Efforts were made to recruit at least 100 patients in each of the following subpopulations: elderly (? 65 years); African-American; Hispanic; patients with T2DM; and patients with metabolic syndrome.	
Investigational product:	AVALIDE	
Dose:	150/12.5 mg tablets	
Administration:	one or two tablets orally per day	

Duration of treatment: 24 weeks

Reference therapy:

Oral Formulation	Manufacturer	Lot	Expiration
Placebo tablets	BMS	8MAE420 3A67533	31-JAN-2006 31-OCT-2006
Hydrochlorothiazide 12.5 mg	Mylan	3L0122 3L0410 3L0493	31-JAN-2005 31-JAN-2005 30-APR-2005

Criteria for evaluation:	
Efficacy:	**Efficacy:** The primary efficacy variable was change in mean SBP from baseline to Week 18. The secondary efficacy variables were: >Change in mean DBP from baseline to Week 18. >Changes in mean SBP and in mean DBP from baseline to Week 10. >SBP and DBP response rates and control rates at Week 10 and at Week 18. >The primary and secondary efficacy variables listed above for each of the subgroups, defined by age, gender, race/ethnicity, metabolic syndrome status, T2DM status, and previous antihypertensive therapy. >Changes in hs-CRP (added by the Statistical Analysis Plan, dated 01 September 2004).
Safety:	**Safety:** Frequency and severity of adverse events (AEs) and significant abnormal laboratory findings.
Summary:	Of the 1005 patients in the safety population, 844 patients commenced HCTZ 12.5 mg treatment and the baseline and demographic characteristics of these patients were analyzed. More patients were female than male (52% versus 48% of patients, respectively). The majority of patients were <65 years (75% of patients) and Caucasian (61% of patients). Most patients were not diagnosed with T2DM (70% of patients), nor with metabolic syndrome (53% of patients). The most common previous antihypertensives were angiotensinconverting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers (34%, 20%, and 20% of patients, respectively). Mean baseline SBP was 154.0 (±10.26) mmHg and mean baseline DBP was 91.3 (±8.82) mmHg. More than 100 patients in each of the subgroups commenced HCTZ 12.5 mg treatment (elderly [65 years]: 212 patients; African-American: 191 patients; Hispanic: 119 patients; T2DM: 254 patients; and metabolic syndrome: 386 patients).
Statistical methods:	Mean, standard deviation, median, minimum and maximum were calculated for continuous variables. Approximate 95% confidence intervals (CIs) were calculated for point estimates of mean change scores in continuous variables. Mean changes from baseline were tested using a paired t-test for a normally distributed population. If the sample data appeared to be selected from a population that was not normally distributed, the Wilcoxon Signed Rank Test was employed. Response and control endpoints were calculated as frequency counts and percentages with associated 95% CIs. Similar statistical analyses were carried on subgroup populations.

Efficacy results:	Mean Change in BP Analysis of the primary efficacy endpoint revealed a substantial significant mean SBP reduction of 21.5 (±14.34) mmHg ($p<0.001$) from baseline to Week 18. Avalide 150/12.5 mg treatment for 8 weeks led to a significant decrease of 15.1 (±12.53) mmHg in SBP, compared with baseline ($p<0.001$) when SBP was measured at Week 10. Avalide 150/12.5 mg led to a significant decrease of 7.2 (±8.03) mmHg in DBP, compared with baseline ($p<0.001$) when DBP was measured at Week 10. Increasing the dose of Avalide to 300/25 mg led to a greater DBP reduction – the total DBP reduction from baseline to Week 18 was 10.4 (±8.65) mmHg ($p<0.001$). BP Response Rates Over the entire study period from baseline to Week 18, a very high proportion of the intent-to-treat (ITT) population (95%) showed a SBP response and 91% showed a DBP response (defined as SBP <140 mmHg [<130 mmHg for patients with diabetes] and DBP <90 mmHg [<80 mmHg for patients with diabetes] or a decrease in SBP or DBP ? 10 mmHg from baseline). At Week 10, study treatment with Avalide (150/12.5 mg) for 8 weeks led to an increase in the proportion of patients achieving a BP response from 26% at Week 2 to 63% at Week 10 for SBP. For DBP, Avalide (150/12.5 mg) treatment led to an increase in the proportion of patients achieving a BP response from 39% at Week 2 to 61% at Week 10. Following 8 weeks of treatment with Avalide (300/25 mg), the proportion of patients achieving a BP response increased to 78% for SBP and 72% for DBP at Week 18. BP Control Rates Over the entire study period from baseline to Week 18, over three-quarters of the ITT population (77%) achieved SBP control and 83% achieved DBP control (control defined as SBP <140 mmHg [<130 mmHg for patients with diabetes] or DBP <90 mmHg [<80 mmHg for patients with diabetes] at the end of the study). Study treatment with Avalide (150/12.5 mg) for 8 weeks led to an increase in the proportion of patients achieving BP control from 2% at Week 2 (while on HCTZ 12.5mg) to 36% at Week 10 for SBP, following treatment with Avalide 150/12.5 mg. For DBP, Avalide (150/12.5 mg) treatment led to an increase in the proportion of patients achieving a DBP control from 36% at Week 2 to 54% at Week 10. Study treatment with Avalide (300/25 mg) for 8 weeks led to a higher proportion of patients achieving BP control. At Week 18, the proportion of patients that achieved control of SBP increased to 54% for SBP and 63% for DBP. Subgroup Analysis Analysis of the primary and secondary efficacy variables for each of the subgroups, defined by age, gender, race/ethnicity, metabolic syndrome status, T2DM status, and previous antihypertensive therapy revealed similar results as those found in the ITT population. Avalide (150/12.5 mg and 300/25 mg) study treatment was effective at significantly lowering both SBP and DBP over the study period in all population subgroups. The proportion of subgroup patients showing a SBP and DPB response and those achieving SBP and DBP control also were similar to the whole ITT population.

Safety results:	All treatments were well tolerated, with most AEs being of mild or moderate intensity and transient in duration. A total of 551 (55%) patients experienced a treatment-emergent AE. During placebo treatment, AEs were reported in 24% of patients. A similar proportion of patients reported AEs during both Avalide (150/12.5 mg and 300/25 mg) treatment periods (27% and 26% of patients, respectively). The most frequent treatment-emergent AE over the entire study period was headache, which occurred in 76 (8%) patients. During Avalide study therapy the most frequent treatment-emergent AE was dizziness, which occurred in 2% of patients during Avalide 150/12.5 mg and in 3% of patients during Avalide 300/25 mg treatment. Drug-related AEs were reported in 14% of patients over the study period. The percentage of patients who discontinued from the study because of AEs was comparable between the treatment regimens (placebo: 1%; HCTZ 12.5 mg: <1%; Avalide 150/12.5 mg: 2%; and Avalide 300/25 mg: 3%). There were a total of 3 deaths, 2 of which occurred during the study period. Patient 020-0009 died during placebo treatment. Post-mortem results revealed that this was caused by a myocardial infarction, brought on by atherosclerotic cardiovascular disease. Patient 020-0016 was involved in a fatal motor vehicle accident during study treatment with Avalide (150/12.5 mg). In addition, one patient died following enrollment, but prior to commencement of any study treatment (patient 133-0019 suffered a cardiac arrest 8 due to natural causes). All deaths during the study were considered unrelated to the study medication. The majority of the SAEs reported during the study were unrelated to the study medication. One patient experienced a SAE of hypotension during Avalide 150/12.5 mg, which was recorded as probably related to the study medication. There were no clinically significant changes in laboratory parameters.
Date of report:	22 December 2004