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New Data Shows Investigational Triple Antihypertensive Combination Therapy Significantly Lowers Blood Pressure in Hard-to-Treat Patients with Hypertension and Diabetes

Efficacy and Safety of the Triple Combination Therapy of Olmesartan Medoxomil / Amlodipine / Hydrochlorothiazide Also Demonstrated in Hispanic/Latino and Obese Patients with High Blood Pressure

Parsippany, NJ – June 28, 2010 – Preliminary results of a pre-specified subgroup study analysis of patients with diabetes and hypertension demonstrated that the investigational triple combination therapy of olmesartan medoxomil / amlodipine / hydrochlorothiazide (40/10/25 mg) resulted in a statistically significant greater Least Squares (LS) mean reduction in blood pressure from baseline at week 12 (37.9/22.0 mm Hg versus 26.4-28.0/14.7-17.6 mm Hg, P≤0.0013) as compared to corresponding dual combination therapy [olmesartan medoxomil (40 mg) / amlodipine (10 mg); olmesartan medoxomil (40 mg) / hydrochlorothiazide (25 mg); or amlodipine (10 mg) and hydrochlorothiazide (25 mg)].[1] Blood pressure is more difficult to control among patients with hypertension and diabetes compared to patients with hypertension alone.[2] These findings were presented today during a poster presentation at the American Diabetes Association (ADA) 70th Annual Scientific Sessions in Orlando, FL.

This analysis of the TRINITY study (**Tri**ple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hyperte**n**s**i**ve Patien**t**s Stud**y**) also demonstrated that the investigational triple combination therapy (40/10/25 mg) enabled more patients with hypertension and diabetes to achieve blood pressure goal of <130/80 mm Hg at week 12 as compared to corresponding dual combination therapies (41.1 percent in the triple combination group versus 10.1 to 16.3 percent in the dual combination groups, P≤0.0002).[1] Baseline blood pressures for those patients receiving the triple combination therapy and corresponding dual combination therapies were 170.7/98.3 mm Hg and 170.7-173.1/97.8-99.3 mm Hg, respectively.[1]

Approximately 70 percent of people with diabetes have high blood pressure,[3] which puts them at greater risk of developing long-term complications such as cardiovascular and renal disease.[2] In order to achieve recommended blood pressure control of <130/80 mm Hg, the majority of people with diabetes are likely to need to take two or more antihypertensive medications.[2]

About 15.5 percent (387 of 2,492) of the entire patient population of the TRINITY study were hypertensive patients with diabetes, and were thus included in this subgroup analysis.[1] In these patients,

the triple combination therapy was well tolerated with most reported adverse events defined as mild or moderate in severity.[1]

"In addition to taking medications to treat high blood pressure, patients with diabetes often need to take several other medications to ensure glucose and cholesterol levels also are within recommended target levels," said Suzanne Oparil, MD, Professor of Medicine and Physiology and Biophysics at the University of Alabama School of Medicine. "Therefore, having a blood pressure-lowering treatment option that combines three medications into one pill will likely help patients take all of their medications as prescribed. Results of this subgroup analysis are important because it shows that this investigational triple combination therapy can help some of the most challenging patients significantly lower their blood pressure."

The triple combination therapy (40/10/25 mg) also demonstrated superior efficacy in the non-diabetes cohort with 68.6 percent of patients achieving goal compared to 39.0 to 52.8 percent in the dual combination therapy groups ($P<0.0001$).[1] Treatment with the triple combination therapy (40/10/25 mg) also resulted in greater LS mean reductions in systolic and diastolic blood pressure in the non-diabetes cohort compared to the dual combination therapy groups (38.5/21.5 mm Hg versus 28.9 to 31.9/14.7 to 17.8 mm Hg, respectively, $p<0.0001$).[1] Mean baseline blood pressure for the non-diabetes cohort was 167.4/101.4 mm Hg in the triple combination therapy group compared to 167.3-168.6/101.2-101.6 mm Hg in the dual combination therapy groups.[1]

Publication-Only Abstract on Ethnicity and BMI Subgroup Analysis

Two additional pre-specified subgroup analyses of the TRINITY study by ethnicity (Hispanic/Latino or non-Hispanic/Non-Latino) and body mass index (BMI) category of <30 kg/m^2 or ≥ 30 kg/m^2 found that the triple combination therapy was similarly more effective than dual regimens, regardless of the ethnicity and BMI of the patient.[4]

It is estimated that hypertension affects 21 percent of Hispanic adults (18 years or older) in the U.S.[5] Additionally, the majority of patients with high blood pressure are overweight, with the condition being six times more frequent in obese people.[6]

Results for the ethnicity subgroup analysis [Hispanic or Latino (n=369, 14.8 percent) and non-Hispanic or non-Latino (n=2,122)] showed that the olmesartan medoxomil / amlodipine / hydrochlorothiazide (40/10/25 mg) triple combination therapy produced a significantly greater mean reduction in seated diastolic blood pressure ($P\leq 0.0236$) and a greater reduction in seated systolic blood pressure from baseline to week 12 compared with each dual combination therapy regardless of ethnicity.[4] Additionally, in both non-obese patients (n=937, BMI of <30 kg/m^2) and obese patients (n=1,555, BMI of ≥ 30 kg/m^2), the triple combination therapy (40/10/25 mg) resulted in significantly greater LS mean reductions in seated diastolic blood pressure ($P\leq 0.0042$) and seated systolic blood pressure ($P\leq 0.0003$) compared with each dual combination group.[4]

Additionally, in both the ethnicity and BMI subgroups of the study, the triple combination of olmesartan medoxomil / amlodipine / hydrochlorothiazide (40/10/25 mg) resulted in a greater percentage of patients reaching blood pressure goal compared with each dual combination group.[4] The incidence of treatment-emergent events in the BMI and ethnicity subgroup analyses was comparable between groups and adverse events were mild or moderate.[4]

TRINITY Study Design

At total of 2,492 patients with moderate to severe hypertension were enrolled into the Phase 3, multicenter, randomized, double-blind, parallel-group study, which examined the safety and efficacy of the triple combination of olmesartan medoxomil / amlodipine / hydrochlorothiazide (40/10/25 mg).[1,4] Patients were randomized to receive one of three dual combination therapies (n=2,456) or placebo (n=36) for the first two weeks of the study: olmesartan medoxomil (40 mg) / amlodipine (10 mg); olmesartan medoxomil (40 mg) / hydrochlorothiazide (25 mg); or, amlodipine (10 mg) / hydrochlorothiazide (25 mg).[1,4] After the first two weeks, until week four, the 36 patients on placebo were switched to one of the dual combination therapies.[1,4] At four weeks, a subset of patients from each of the three dual combination groups were switched to the triple combination therapy of olmesartan (40 mg) / amlodipine (10 mg) / hydrochlorothiazide (25 mg) and continued for 12 weeks (n=627).[1,4] The 12 week double-blind treatment period was followed by a 40 week open-label treatment period.[1,4] The 12-week results were presented at the American Society of Hypertension (ASH) annual meeting earlier this year, which found that the blood pressure-lowering and percentage of patients reaching the current recommended blood pressure target was greater with the triple combination therapy (40/10/25 mg) versus corresponding dual combination therapy regardless of gender, age, race, and hypertension severity ($P<0.0001$).[7]

Safety & Tolerability

Across all groups, drug-related treatment adverse events (TEAEs) were reported in 25.4 percent of patients.[1] Most TEAEs and drug-related TEAEs were mild or moderate in severity.[1] More discontinuations due to TEAEs occurred in the olmesartan medoxomil / amlodipine / hydrochlorothiazide (40/10/25 mg) (4.0 percent) versus the dual combination therapy groups (1.0 to 2.1 percent) and were due to adverse events such as dizziness and hypotension.[1] These discontinuations can potentially be attributed to the more pronounced pharmacodynamic effect of the triple combination therapy.[1] Peripheral edema also was a cause for discontinuation.[1]

In addition, discontinuations for patients on triple combination therapy also included subjects who experienced an adverse event on earlier treatment (i.e. placebo or dual), prior to initiation of the triple combination regimen.[1]

About The Triple Combination Therapy

A fixed-dose, single combination product of olmesartan medoxomil/ amlodipine / hydrochlorothiazide is currently under review for approval with the US Food and Drug Administration (FDA) for the treatment of hypertension.

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