ID: TAK-491CLD_308 Safety and Tolerability of Azilsartan Medoxomil Plus Chlorthalidone Compared to Olmesartan Medoxomil Plus Hydrochlorothiazide in Participants With Essential Hypertension NCT00996281

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Participant Flow

Recruitment Details	Participants took part in the study at 79 investigative sites in the United States, Netherlands, Poland, the United Kingdom and Germany from 27 October 2009 to 17 November 2011.
Pre-Assignment Details	Participants with a diagnosis of essential hypertension were randomized to receive open-label treatment with either Azilsartan Medoxomil and Chlorthalidone or Olmesartan Medoxomil and Hydrochlorothiazide for up to 52 weeks.

Arm/Group Title	Azilsartan Medoxomil and Chlorthalidone	Olmesartan Medoxomil and Hydrochlorothiazide	Total (Not public)
Arm/Group Description	Azilsartan medoxomil 40 mg and chlorthalidone 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of azilsartan medoxomil 80 mg and chlorthalidone 25 mg. Additional antihypertensive agents could be added as needed to achieve blood pressure control.	Participants in the United States: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of Olmesartan medoxomil 40 mg and hydrochlorothiazide 25 mg. Participants in Europe: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of Olmesartan medoxomil 20 mg and hydrochlorothiazide 25 mg. Additional antihypertensive agents could be added as needed to achieve blood pressure control.	
Period Title: Overall Study			
Started	418	419	837

Completed	287	330	617
Not Completed	131	89	220
Reason Not Completed			
Adverse Event	75	37	112
Major Protocol Deviation	6	7	13
Lost to Follow-up	14	16	30
Withdrawal by Subject	31	20	51
Lack of Efficacy	0	2	2
Other	5	7	12
NOTE : "Other" is not sufficiently descriptive for "Other" Reason Not Completed. Please provide a more descriptive label.			
(Not Public)	Not Completed = 131 Total from all reasons = 131	Not Completed = 89 Total from all reasons = 89	

Baseline Characteristics

Arm/Group Title	**Azilsartan Medoxomil and Chlorthalidone**	**Olmesartan Medoxomil and Hydrochlorothiazide**	**Total**
Arm/Group Description	Azilsartan medoxomil 40 mg and chlorthalidone 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of azilsartan medoxomil 80 mg and chlorthalidone 25 mg. Additional antihypertensive agents could be added as needed to achieve blood pressure control.	Participants in the United States: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of Olmesartan medoxomil 40 mg and hydrochlorothiazide 25 mg. Participants in Europe: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of Olmesartan medoxomil 20 mg and hydrochlorothiazide 25 mg. Additional antihypertensive agents could be added as needed to achieve blood pressure control.	
Overall Number of Baseline Participants	418	419	**837**
Baseline Analysis Population Description			

[Not specified]			
Age, Continuous			
Mean (Standard Deviation)			
Units: years	58.5 (10.79)	57.6 (10.80)	58.1 (10.80)
Age, Customized			
Measure Type: Number			
Units: participants			
<45 years	46	48	94
45 to 64 years	251	259	510
65 to 74 years	94	93	187
≥75 years	27	19	46
Gender, Male/Female			
Measure Type: Number			
Units: participants			
Female	192	173	365
Male	226	246	472
Race/Ethnicity, Customized [1]			
Measure Type: Number			
Units: participants			
Hispanic or Latino	40	41	81
Non-Hispanic or Latino	209	205	414
Not collected	169	172	341
Missing	0	1	1

[1] Ethnicity was only collected from U.S. sites.

Race/Ethnicity, Customized [1]			
Measure Type: Number			
Units: participants			
American Indian or Alaska Native	4	5	9
	NOTE : The sum of participants in all Categories for the Measure does not equal the Overall Number of Baseline Participants in the Arm/Group.	NOTE : The sum of participants in all Categories for the Measure does not equal the Overall Number of Baseline Participants in the Arm/Group.	
Asian	4	7	11
Black or African American	72	74	146
Native Hawaiian or Other Pacific Islander	0	0	0
White	341	336	677
Multiracial	3	3	6

[1] Participants could choose more than 1 category for race. Participants who choose more than 1 race category are included in each category indicated and are also included in the multiracial category.

Region of Enrollment			
Measure Type: Number			
Units: participants			
Poland	52	54	106
United States	249	247	496
Netherlands	56	58	114
Germany	22	21	43
United Kingdom	39	39	78

Height			
Mean (Standard Deviation)			169.8
Units: cm	169.9 (10.2)	169.6 (10.1)	(10.1)
Weight			
Mean (Standard Deviation)			91.50
Units: kg	91.00 (21.025)	92.00 (21.727)	(21.373)
Body Mass Index (BMI)			
Mean (Standard Deviation)			31.7
Units: kg/m^2	31.4 (6.21)	31.9 (6.63)	(6.42)
Smoking history			
Measure Type: Number			
Units: participants			
Never smoked	214	205	419
Current smoker	82	78	160
Ex-smoker	122	136	258
Diabetes Status			
Measure Type: Number			
Units: participants			
Yes	64	59	123
No	354	360	714
Estimated glomerular filtration rate			
Measure Type: Number			
Units: participants			
Moderate impairment: ≥30 and <60 ml/min/1.73 m^2	54	43	97
Mild impairment: ≥60 and <90 ml/min/1.73 m^2	275	265	540
Normal: ≥90 ml/min/1.73 m^2	87	110	197
Missing	2	1	3
Chronic Kidney Disease (CKD) status [1]			
Measure Type: Number			
Units: participants			
Yes	59	51	110
No	359	368	727
Systolic blood pressure			
Measure Type: Number			
Units: participants			
≥140 - < 160 mmHg	1	1	2
≥160 - < 180 mmHg	382	385	767
≥180 mm Hg	35	33	68
Diastolic blood pressure			
Measure Type: Number			
Units: participants			
< 90 mmHg	107	103	210
≥90 mmHg	311	316	627

[1] Participants were considered to have CKD if their estimated glomerular filtration rate (GFR) was <60 mL/min/1.73 m^2 or urinary albumin:creatinine ratio (UACR) was >200 mg albumin/g creatinine at Screening.

Outcome Measures

1. Primary Outcome

Title: Percentage of Participants With at Least 1 Adverse Event

Description: An adverse event is defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product without regard to causality.

Time Frame: From Week 0 (Day 1) to Week 52.

Safety Issue? Yes

Outcome Measure Data

Analysis Population Description

Safety analysis set: All participants who received at least 1 dose of study medication.

Arm/Group Title	**Azilsartan Medoxomil and Chlorthalidone**	**Olmesartan Medoxomil and Hydrochlorothiazide**
Arm/Group Description:	Azilsartan medoxomil 40 mg and chlorthalidone 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of azilsartan medoxomil 80 mg and chlorthalidone 25 mg. Additional antihypertensive agents could be added as needed to achieve blood pressure control.	Participants in the United States: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of Olmesartan medoxomil 40 mg and hydrochlorothiazide 25 mg. Participants in Europe: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of Olmesartan medoxomil 20 mg and hydrochlorothiazide 25 mg. Additional antihypertensive agents could be added as needed to achieve blood pressure control.
Number of Participants Analyzed	418	419
Measure Type: Number Units: percentage of participants	78.5	76.4

2. Secondary Outcome

Title: Percentage of Participants With Serum Creatinine Elevations Greater Than 50% From Baseline and Greater Than the Upper Limit of Normal (ULN)

Description: Serum creatinine was measured at every visit and evaluated as a laboratory parameter of special interest. The percentage of participants with creatinine increase ≥50% from Baseline and greater than ULN was summarized: - At any visit (includes transient and persistent elevations). - At the Final Visit (includes persistent elevations and participants whose first elevation may have been at the Final Visit). - At least 2 consecutive visits (includes only persistent elevations).

Time Frame: Baseline and Week 52

Safety Issue? Yes

Outcome Measure Data

Analysis Population Description

Safety analysis set.

Arm/Group Title	**Azilsartan Medoxomil and Chlorthalidone**	**Olmesartan Medoxomil and Hydrochlorothiazide**
Arm/Group Description:	Azilsartan medoxomil 40 mg and chlorthalidone 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of azilsartan medoxomil 80 mg and chlorthalidone 25 mg. Additional antihypertensive agents could be added as needed to achieve blood pressure control.	Participants in the United States: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of Olmesartan medoxomil 40 mg and hydrochlorothiazide 25 mg. Participants in Europe: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of Olmesartan medoxomil 20 mg and hydrochlorothiazide 25 mg. Additional antihypertensive agents could be added as needed to achieve blood pressure control.
Number of Participants Analyzed	418	419
Measure Type: Number Units: percentage of participants		
At any postbaseline visit	14.2	5.8
at the Final Visit	5.9	1.0
≥2 consecutive elevations	5.1	1.2

Adverse Events

Time Frame	Treatment-emergent adverse events are adverse events that started after the first dose of double-blind study drug and no more than 14 days (or 30 days for a serious adverse event) after the last dose of study drug.
Additional Description	At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.
Source Vocabulary Name	MedDRA (14.0)
Assessment Type	Systematic Assessment

Arm/Group Title	Azilsartan Medoxomil and Chlorthalidone	Olmesartan Medoxomil and Hydrochlorothiazide
Arm/Group Description	Azilsartan medoxomil 40 mg and chlorthalidone 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of azilsartan medoxomil 80 mg and chlorthalidone 25 mg. Additional antihypertensive agents could be added as needed to achieve blood pressure control.	Participants in the United States: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of Olmesartan medoxomil 40 mg and hydrochlorothiazide 25 mg. Participants in Europe: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg combination tablet, orally, once daily for up to 52 weeks. For participants who did not achieve target blood pressure by Week 4, titration to a maximum dose of Olmesartan medoxomil 20 mg and hydrochlorothiazide 25 mg. Additional antihypertensive agents could be added as needed to achieve blood pressure control.

Serious Adverse Events

	Azilsartan Medoxomil and Chlorthalidone Affected / at Risk (%)	**Olmesartan Medoxomil and Hydrochlorothiazide** Affected / at Risk (%)
Total	24/418 (5.74%)	26/419 (6.21%)
Cardiac disorders		
Angina pectoris † A	0/418 (0%)	2/419 (0.48%)
Atrial fibrillation † A	1/418 (0.24%)	1/419 (0.24%)
Cardiac arrest † A	1/418 (0.24%)	0/419 (0%)

† A

Cardiogenic shock	1/418 (0.24%)	0/419 (0%)
Coronary artery disease † A	0/418 (0%)	1/419 (0.24%)
Mitral valve incompetence † A	1/418 (0.24%)	0/419 (0%)
Myocardial infarction † A	0/418 (0%)	1/419 (0.24%)
Congenital, familial and genetic disorders		
Hydrocele † A	1/418 (0.24%)	0/419 (0%)
Ear and labyrinth disorders		
Vertigo † A	0/418 (0%)	1/419 (0.24%)
Gastrointestinal disorders		
Colitis ulcerative † A	1/418 (0.24%)	0/419 (0%)
Gastritis † A	0/418 (0%)	1/419 (0.24%)
Hemorrhoid † A	0/418 (0%)	1/419 (0.24%)
Pancreatitis acute † A	1/418 (0.24%)	0/419 (0%)
Rectal hemorrhage † A	0/418 (0%)	1/419 (0.24%)
General disorders		
Drowning † A	1/418 (0.24%)	0/419 (0%)
Non-cardiac chest pain † A	1/418 (0.24%)	2/419 (0.48%)
Hepatobiliary disorders		
Biliary colic † A	1/418 (0.24%)	0/419 (0%)
Cholelitiasis † A	1/418 (0.24%)	0/419 (0%)
Infections and infestations		
Bronchitis † A	1/418 (0.24%)	0/419 (0%)
Bronchopneumonia † A	1/418 (0.24%)	0/419 (0%)
Cellulitis † A	0/418 (0%)	1/419 (0.24%)
Diverticulitis † A	0/418 (0%)	1/419 (0.24%)
Endocarditis † A	1/418 (0.24%)	0/419 (0%)
Pneumonia † A	0/418 (0%)	2/419 (0.48%)
Postoperative wound infection † A	1/418 (0.24%)	0/419 (0%)
Rectal abscess † A	0/418 (0%)	1/419 (0.24%)
Sepsis † A	1/418 (0.24%)	0/419 (0%)
Septic shock † A	2/418 (0.48%)	0/419 (0%)
Urinary tract infection † A	1/418 (0.24%)	0/419 (0%)
Injury, poisoning and procedural complications		
Clavicle fracture † A	0/418 (0%)	1/419 (0.24%)
Contusion † A	1/418 (0.24%)	0/419 (0%)
Femur fracture † A	0/418 (0%)	1/419 (0.24%)
Fibula fracture † A	0/418 (0%)	1/419 (0.24%)
Gun shot wound † A	0/418 (0%)	1/419 (0.24%)
Head injury † A	1/418 (0.24%)	0/419 (0%)
Hip fracture † A	0/418 (0%)	1/419 (0.24%)
Joint dislocation † A	1/418 (0.24%)	0/419 (0%)
Rib fracture † A	0/418 (0%)	1/419 (0.24%)
Road traffic accident † A	1/418 (0.24%)	2/419 (0.48%)
Skeletal injury † A	1/418 (0.24%)	0/419 (0%)
Tibia fracture † A	0/418 (0%)	1/419 (0.24%)
Wound secretion † A	1/418 (0.24%)	0/419 (0%)
Investigations		

Blood creatinine increased † A	0/418 (0%)	2/419 (0.48%)
Musculoskeletal and connective tissue disorders		
Back pain † A	1/418 (0.24%)	1/419 (0.24%)
Intervertebral disc protrusion † A	2/418 (0.48%)	0/419 (0%)
Lumbar spinal stenosis † A	1/418 (0.24%)	0/419 (0%)
Osteoarthritis † A	1/418 (0.24%)	1/419 (0.24%)
Pseudarthrosis † A	1/418 (0.24%)	0/419 (0%)
Vertebral foraminal stenosis † A	1/418 (0.24%)	0/419 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bladder transitional cell carcinoma † A	0/418 (0%)	1/419 (0.24%)
Breast cancer † A	1/418 (0.24%)	0/419 (0%)
Breast cancer stage II † A	0/418 (0%)	1/419 (0.24%)
Malignant melanoma † A	1/418 (0.24%)	0/419 (0%)
Prostate cancer † A	1/418 (0.24%)	0/419 (0%)
Renal cancer † A	1/418 (0.24%)	0/419 (0%)
Nervous system disorders		
Loss of consciousness † A	1/418 (0.24%)	0/419 (0%)
Presyncope † A	0/418 (0%)	1/419 (0.24%)
Radicular syndrome † A	1/418 (0.24%)	0/419 (0%)
Syncope † A	2/418 (0.48%)	0/419 (0%)
Transient ischaemic attack † A	0/418 (0%)	1/419 (0.24%)
Psychiatric disorders		
Major depression † A	1/418 (0.24%)	0/419 (0%)
Renal and urinary disorders		
Renal failure acute † A	0/418 (0%)	1/419 (0.24%)
Reproductive system and breast disorders		
Rectocele † A	1/418 (0.24%)	0/419 (0%)
Respiratory, thoracic and mediastinal disorders		
Bronchitis chronic † A	0/418 (0%)	1/419 (0.24%)
Chronic obstructive pulmonary disease † A	1/418 (0.24%)	1/419 (0.24%)
Interstitial lung disease † A	0/418 (0%)	1/419 (0.24%)
Pulmonary embolism † A	2/418 (0.48%)	0/419 (0%)
Pulmonary mass † A	0/418 (0%)	1/419 (0.24%)
Respiratory failure † A	0/418 (0%)	1/419 (0.24%)
Vascular disorders		
Arteriosclerosis † A	0/418 (0%)	1/419 (0.24%)
Orthostatic hypotension † A	1/418 (0.24%)	0/419 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (14.0)

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting	5%

Other Adverse Events

	Azilsartan Medoxomil and Chlorthalidone	Olmesartan Medoxomil and Hydrochlorothiazide
	Affected / at Risk (%)	Affected / at Risk (%)
Total	217/418 (51.91%)	183/419 (43.68%)
Gastrointestinal disorders		
Diarrhoea † A	20/418 (4.78%)	21/419 (5.01%)
Nausea † A	20/418 (4.78%)	21/419 (5.01%)
General disorders		
Fatigue † A	21/418 (5.02%)	17/419 (4.06%)
Infections and infestations		
Nasopharyngitis † A	51/418 (12.2%)	48/419 (11.46%)
Upper respiratory tract infection † A	20/418 (4.78%)	27/419 (6.44%)
Investigations		
Blood creatinine increased † A	90/418 (21.53%)	35/419 (8.35%)
Nervous system disorders		
Dizziness † A	68/418 (16.27%)	53/419 (12.65%)
Headache † A	31/418 (7.42%)	46/419 (10.98%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (14.0)

Limitations and Caveats

[Not Specified]

More Information

Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The first study related publication will be a multi-center publication submitted within 24 months after conclusion or termination of a study at all sites. After such multi site publication, all proposed site publications and presentations will be submitted to sponsor for review 60 days in advance of publication. Site will remove Sponsor confidential information unrelated to study results. Sponsor can delay a proposed publication for another 60 days to preserve intellectual property.

Results Point of Contact

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