ID: TAK-491CLD_309 Long-Term Safety of Azilsartan Medoxomil and Chlorthalidone Compared to Olmesartan Medoxomil and Hydrochlorothiazide in Participants With Hypertension and Kidney Disease NCT01309828

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Participant Flow

Recruitment Details	Participants took part in the study at 46 investigative sites in the United States, Germany, Latvia, Lithuania, Poland, Slovakia, and the Ukraine from 02 March 2011 to 11 October 2012.
Pre-Assignment Details	Participants with high blood pressure and moderate renal impairment were enrolled in 1 of 2 once-daily (QD) treatment groups.

Arm/Group Title	**Azilsartan Medoxomil + Chlorthalidone**	**Olmesartan Medoxomil + Hydrochlorothiazide**	Total (Not public)
Arm/Group Description	United States and Europe: Azilsartan medoxomil 20 mg plus chlorthalidone 12.5 mg fixed dose combination tablets (TAK-491CLD), titrated up to azilsartan medoxomil 40 mg plus chlorthalidone 25 mg orally, once daily for up to 52 weeks.	United States: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets (OLM/HCTZ), titrated up to olmesartan medoxomil 40 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks. Europe: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets, titrated up to olmesartan medoxomil 20 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks.	
Period Title: Overall Study			
Started	77	76	153
Completed	61	60	121
Not Completed	16	16	32
Reason Not Completed			
Adverse Event	10	11	21
Voluntary Withdrawal	5	4	9
Major Protocol Deviation	0	1	1
Other	1	0	1

NOTE : "Other" is not

sufficiently descriptive for "Other" Reason Not Completed. Please provide a more descriptive label.		
(Not Public)	Not Completed = 16 Total from all reasons = 16	Not Completed = 16 Total from all reasons = 16

Baseline Characteristics

Arm/Group Title	**Azilsartan Medoxomil + Chlorthalidone**	**Olmesartan Medoxomil + Hydrochlorothiazide**	**Total**
Arm/Group Description	United States and Europe: Azilsartan medoxomil 20 mg plus chlorthalidone 12.5 mg fixed dose combination tablets (TAK-491CLD), titrated up to azilsartan medoxomil 40 mg plus chlorthalidone 25 mg orally, once daily for up to 52 weeks.	United States: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets (OLM/HCTZ), titrated up to olmesartan medoxomil 40 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks. Europe: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets, titrated up to olmesartan medoxomil 20 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks.	
Overall Number of Baseline Participants	77	76	**153**
Baseline Analysis Population Description	[Not specified]		
Age, Continuous **Mean (Standard Deviation)** **Units: years**	67.9 (8.24)	68.9 (9.10)	68.4 (8.66)
Age, Customized **Measure Type: Number** **Units: participants**			
<45 years	0	1	1
≥45 to <65 years	21	18	39
≥65 to <75 years	38	39	77
≥75 years	18	18	36
Gender, Male/Female **Measure Type: Number** **Units: participants**			
Female	45	31	76
Male	32	45	77
Race/Ethnicity, Customized **Measure Type: Number** **Units: participants**			
White	57	62	119
Black or African American	18	12	30

Asian	2	2	4
Region of Enrollment			
Measure Type: Number			
Units: participants			
Germany	10	9	19
Latvia	4	5	9
Lithuania	5	2	7
Poland	7	6	13
Slovakia	6	6	12
Ukraine	6	11	17
United States	39	37	76
Weight			
Mean (Standard Deviation)			
Units: kg	83.54 (17.894)	90.14 (21.587)	86.82 (20.025)
Height			
Mean (Standard Deviation)			
Units: cm	165.7 (9.65)	168.7 (9.48)	167.2 (9.65)
Body Mass Index (BMI)			
Mean (Standard Deviation)			
Units: kg/m^2	30.44 (6.226)	31.57 (6.524)	31.00 (6.380)
Smoking Classification			
Measure Type: Number			
Units: participants			
Never Smoked	46	40	86
Current Smoker	11	11	22
Ex-smoker	20	25	45
Diabetes Status			
Measure Type: Number			
Units: participants			
Yes	33	32	65
No	44	44	88
Estimated glomerular filtration rate (eGFR)			
Mean (Standard Deviation)			
Units: mL/min/1.73 m^2	48.25 (10.205)	47.73 (8.761)	47.99 (9.487)
Baseline estimated glomerular filtration rate (eGFR) category			
Measure Type: Number			
Units: participants			
≥45 and <60 mL/min/1.73 m^2	40	39	79
≥30 and <45 mL/min/1.73 m^2	31	33	64
≥60 mL/min/1.73 m^2	6	4	10
Systolic blood pressure			
Mean (Standard Deviation)			
Units: mm Hg	151.1 (10.30)	149.0 (7.80)	150.1 (9.18)
Diastolic blood pressure			
Mean (Standard Deviation)			
Units: mm Hg	84.8 (10.31)	84.7 (9.68)	84.7 (9.97)
Systolic blood pressure categories			
Measure Type: Number			

Units: participants			
<140 mm Hg	11	10	21
≥140 to <160 mm Hg	60	64	124
≥160 to <180 mm Hg	5	2	7
≥180 mm Hg	1	0	1
Diastolic blood pressure categories			
Measure Type: Number			
Units: participants			
<90 mm Hg	52	50	102
≥90 mm Hg	25	26	51

Outcome Measures

1. Primary Outcome

Title: Number of Participants With at Least 1 Adverse Event (AE)

Description: An AE is any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have a causal relationship with this treatment. A serious AE is defined as any untoward medical occurrence that resulted in death, was life threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability or incapacity, led to a congenital anomaly/birth defect or was an important medical event that may have required intervention to prevent any of items above.

Time Frame: From the first dose of open-label study drug until 14 days (or 30 days for a serious adverse event) after the last dose of open- label study drug (up to 56 weeks).

Safety Issue? Yes

Outcome Measure Data

Analysis Population Description

Safety analysis set - All participants who received at least 1 dose of open-label study drug.

Arm/Group Title	**Azilsartan Medoxomil + Chlorthalidone**	**Olmesartan Medoxomil + Hydrochlorothiazide**
Arm/Group Description:	United States and Europe: Azilsartan medoxomil 20 mg plus chlorthalidone 12.5 mg fixed dose combination tablets (TAK-491CLD), titrated up to azilsartan medoxomil 40 mg plus chlorthalidone 25 mg orally, once daily for up to 52 weeks.	United States: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets (OLM/HCTZ), titrated up to olmesartan medoxomil 40 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks. Europe: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets, titrated up to olmesartan medoxomil 20 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks.

Number of Participants Analyzed	77	76
Measure Type: Number Units: participants		
Adverse Events	68	58
Adverse Events Leading to Discontinuation	17	15
Serious Adverse Events	8	9
Serious Adverse Events Leading to Discontinuation	5	4
Death	0	1

2. Secondary Outcome

Title: Percentage of Participants at Final Visit Who Achieve Target Systolic Blood Pressure <130 mm Hg

Description: Systolic blood pressure is the arithmetic mean of the 3 serial sitting systolic blood pressure measurements. Percentage of participants who achieve a sitting clinic systolic blood pressure response defined as less than 130 mm Hg at Week 52.

Time Frame: Week 52

Safety Issue? No

Outcome Measure Data

Analysis Population Description

Full analysis set participants (all randomized participants who received at least 1 dose of open-label study drug) with both Baseline and a post-baseline value; last observation carried forward was used.

Arm/Group Title	**Azilsartan Medoxomil + Chlorthalidone**	**Olmesartan Medoxomil + Hydrochlorothiazide**
Arm/Group Description:	United States and Europe: Azilsartan medoxomil 20 mg plus chlorthalidone 12.5 mg fixed dose combination tablets (TAK-491CLD), titrated up to azilsartan medoxomil 40 mg plus chlorthalidone 25 mg orally, once daily for up to 52 weeks.	United States: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets (OLM/HCTZ), titrated up to olmesartan medoxomil 40 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks. Europe: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets, titrated up to olmesartan medoxomil 20 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks.
Number of Participants Analyzed	75	74
Number (95% Confidence Interval) Units: percentage of participants	69.3 (57.6 to 79.5)	78.4 (67.3 to 87.1)

3. Secondary Outcome

Title: Percentage of Participants at Final Visit Who Achieved Target Diastolic Blood Pressure <80 mm Hg

Description: Diastolic blood pressure is the arithmetic mean of the 3 serial sitting diastolic blood pressure measurements. Percentage of participants at Week 52 who achieved a sitting clinic diastolic blood pressure response, defined as less than 80 mm Hg.

Time Frame: Week 52

Safety Issue? No

Outcome Measure Data

Analysis Population Description

Full analysis set participants (all randomized participants who received at least 1 dose of open-label study drug) with both Baseline and a post-baseline value; last observation carried forward was used.

Arm/Group Title	**Azilsartan Medoxomil + Chlorthalidone**	**Olmesartan Medoxomil + Hydrochlorothiazide**
Arm/Group Description:	United States and Europe: Azilsartan medoxomil 20 mg plus chlorthalidone 12.5 mg fixed dose combination tablets (TAK-491CLD), titrated up to azilsartan medoxomil 40 mg plus chlorthalidone 25 mg orally, once daily for up to 52 weeks.	United States: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets (OLM/HCTZ), titrated up to olmesartan medoxomil 40 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks. Europe: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets, titrated up to olmesartan medoxomil 20 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks.
Number of Participants Analyzed	75	74
Number (95% Confidence Interval) Units: percentage of participants	80.0 (69.2 to 88.4)	87.8 (78.2 to 94.3)

4. Secondary Outcome

Title: Percentage of Participants at Final Visit Who Achieved Both a Clinic Systolic and Diastolic Blood Pressure Response

Description: Systolic/diastolic blood pressure is the arithmetic mean of the 3 serial sitting systolic/diastolic blood pressure measurements. Percentage of participants who achieved both a sitting clinic systolic and diastolic blood pressure response, defined as systolic blood pressure less than 130 mm Hg and diastolic blood pressure less than 80 mm Hg at Week 52.

Time Frame: Week 52

Safety Issue? No

Outcome Measure Data

Analysis Population Description

Full analysis set participants (all randomized participants who received at least 1 dose of open-label study drug) with both Baseline and a post-baseline value; last observation carried forward was used.

Arm/Group Title	**Azilsartan Medoxomil + Chlorthalidone**	**Olmesartan Medoxomil + Hydrochlorothiazide**
Arm/Group Description:	United States and Europe: Azilsartan medoxomil 20 mg plus chlorthalidone 12.5 mg fixed dose combination tablets (TAK-491CLD), titrated up to azilsartan medoxomil 40 mg plus chlorthalidone 25 mg orally, once daily for up to 52 weeks.	United States: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets (OLM/HCTZ), titrated up to olmesartan medoxomil 40 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks. Europe: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets, titrated up to olmesartan medoxomil 20 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks.
Number of Participants Analyzed	75	74
Number (95% Confidence Interval) Units: percentage of participants	58.7 (46.7 to 69.9)	73.0 (61.4 to 82.6)

Adverse Events

Time Frame	From the first dose of open-label study drug until 14 days (or 30 days for a serious adverse event) after the last dose of open-label study drug (up to 56 weeks). At each visit the investigator had to document any occurrence of

Additional Description	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 15.0
Assessment Type	Systematic Assessment

Arm/Group Title	Azilsartan Medoxomil + Chlorthalidone	Olmesartan Medoxomil + Hydrochlorothiazide
Arm/Group Description	United States and Europe: Azilsartan medoxomil 20 mg plus chlorthalidone 12.5 mg fixed dose combination tablets (TAK-491CLD), titrated up to azilsartan medoxomil 40 mg plus chlorthalidone 25 mg orally, once daily for up to 52 weeks.	United States: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets (OLM/HCTZ), titrated up to olmesartan medoxomil 40 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks. Europe: Olmesartan medoxomil 20 mg plus hydrochlorothiazide 12.5 mg fixed dose combination tablets, titrated up to olmesartan medoxomil 20 mg plus hydrochlorothiazide 25 mg orally, once daily for up to 52 weeks.

Serious Adverse Events

	Azilsartan Medoxomil + Chlorthalidone Affected / at Risk (%)	**Olmesartan Medoxomil + Hydrochlorothiazide** Affected / at Risk (%)
Total	8/77 (10.39%)	9/76 (11.84%)
Cardiac disorders		
Angina pectoris † A	0/77 (0%)	2/76 (2.63%)
Angina unstable † A	2/77 (2.6%)	1/76 (1.32%)
Atrial tachycardia † A	0/77 (0%)	1/76 (1.32%)
Bradycardia † A	0/77 (0%)	1/76 (1.32%)
Coronary artery disease † A	2/77 (2.6%)	1/76 (1.32%)
Gastrointestinal disorders		
Vomiting † A	0/77 (0%)	1/76 (1.32%)
General disorders		
Device malfunction † A	1/77 (1.3%)	0/76 (0%)
Infections and infestations		
Gastroenteritis salmonella † A	1/77 (1.3%)	0/76 (0%)
Injury, poisoning and procedural complications		
Concussion † A	0/77 (0%)	1/76 (1.32%)
Hip fracture † A	0/77 (0%)	1/76 (1.32%)
Metabolism and nutrition disorders		
Diabetes mellitus † A	0/77 (0%)	1/76 (1.32%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Pituitary tumour recurrent † A	0/77 (0%)	1/76 (1.32%)

Nervous system disorders		
Cervicobrachial syndrome † A	1/77 (1.3%)	0/76 (0%)
Hypoglycaemic coma † A	1/77 (1.3%)	0/76 (0%)
Renal and urinary disorders		
Renal failure acute † A	1/77 (1.3%)	0/76 (0%)
Respiratory, thoracic and mediastinal disorders		
Pulmonary artery thrombosis † A	0/77 (0%)	1/76 (1.32%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 15.0

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%	
	Azilsartan Medoxomil + Chlorthalidone Affected / at Risk (%)	**Olmesartan Medoxomil + Hydrochlorothiazide** Affected / at Risk (%)
Total	52/77 (67.53%)	41/76 (53.95%)
Gastrointestinal disorders		
Diarrhoea † A	1/77 (1.3%)	4/76 (5.26%)
General disorders		
Asthenia † A	3/77 (3.9%)	4/76 (5.26%)
Infections and infestations		
Bronchitis † A	4/77 (5.19%)	3/76 (3.95%)
Pharygitis † A	0/77 (0%)	4/76 (5.26%)
Investigations		
Blood creatinine increased † A	34/77 (44.16%)	29/76 (38.16%)
Metabolism and nutrition disorders		
Hyperuricaemia † A	3/77 (3.9%)	4/76 (5.26%)
Hypokalaemia † A	4/77 (5.19%)	3/76 (3.95%)
Nervous system disorders		
Dizziness † A	6/77 (7.79%)	5/76 (6.58%)
Headache † A	8/77 (10.39%)	2/76 (2.63%)
Vascular disorders		
Hypotension † A	4/77 (5.19%)	3/76 (3.95%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 15.0

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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