Clinical trial results:
A Randomized, Double-Blind, Efficacy and Safety Study of AR 14 (AZILSARTAN MEDOXOMIL) Treatment and Withdrawal, Followed by an Open-Label Extension, in Children 6 to Less Than 18 Years of Age With Hypertension

Summary

EudraCT number	2014-000674-18
Trial protocol	HU IT BG
Global end of trial date	11 November 2019

Results information

Result version number	v1 (current)
This version publication date	29 May 2022
First version publication date	29 May 2022

Trial information

Trial identification

Sponsor protocol code	AR14.001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02235909
WHO universal trial number (UTN)	U1111-1162-3595

Notes:

Sponsors

Sponsor organisation name	Arbor Pharmaceuticals, LLC
Sponsor organisation address	6 Concourse Parkway Suite 1800, Atlanta, United States, GA 30328
Public contact	Steven Caras, M.D., Ph.D, Arbor Pharmaceuticals, LLC, Steven.Caras@arborpharma.com
Scientific contact	Steven Caras, M.D., Ph.D, Arbor Pharmaceuticals, LLC, Steven.Caras@arborpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000237-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to evaluate the antihypertensive effect of azilsartan medoxomil (AZM) compared with placebo after a randomized, double-blind, withdrawal (Withdrawal Phase).

Protection of trial subjects:

All parents/legal guardians were required to read and sign an Informed Consent Form for participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	South Africa: 35
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Ukraine: 15
Country: Number of subjects enrolled	United States: 38
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Hungary: 44
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Poland: 26
Worldwide total number of subjects	215
EEA total number of subjects	87

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	49
Adolescents (12-17 years)	166
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 67 investigative sites in Argentina, Brazil, Bulgaria, Colombia, Hungary, Italy, Mexico, Poland, South Africa, Turkey, Ukraine, and the United States from 30 March 2015 to 11 November 2019.

Pre-assignment

Screening details:

Participants with hypertension first initially participated in the Run-in Phase/Washout Phase (Days -28 to 1), following that 215 participants were enrolled in Double-blind (DB) Phase, following DB Phase, 203 participants were enrolled in Withdrawal (WD) Phase and following WD Phase, 197 participants were enrolled in the Open-label (OL) Phase.

Period 1

Period 1 title	Double-Blind Phase (Up to Week 6)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	DB Phase: Losartan 25 mg + 50 mg + 100 mg

Arm description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive the losartan in the DB Phase. Participants with body weight >=25 to <50 kg were randomized to receive losartan 25 mg orally once daily, from Weeks 0 to 2 and losartan 50 mg from Weeks 2 to 6 and participants with body weight >=50 kg received losartan orally once daily 50 mg, from Weeks 0 to 2 and losartan 100 mg from Weeks 2 to 6 in the DB Phase.

Arm type	Active comparator
Investigational medicinal product name	Losartan potassium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Losartan over encapsulated tablets, 25 mg, orally

Investigational medicinal product name	Losartan potassium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Losartan over encapsulated tablets, 50 mg, orally

Investigational medicinal product name	Losartan potassium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Losartan over encapsulated tablets, 100 mg, orally

Arm title	DB Phase: Low-Dose Azilsartan Medoxomil (AZM-L) 10 mg

Arm description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive the low-dose AZM-L DB Phase. Participants with body weight >= 25 to <50 kg or >= 50 kg received AZM-L 10 mg, orally, once daily from Week 0-6 in the DB Phase.

Arm type	Experimental
Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 10 mg, orally

Arm title	DB Phase: AZM-M 10 mg+20 mg

Arm description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive Intermediate-Dose Azilsartan Medoxomil (AZM-M) in the DB Phase. Participants with body weight >=25 to <50 kg or >=50 kg received AZM-M orally, once daily 10 mg from Weeks 0-2 and AZM-M 20 mg from Weeks 2-6 in the DB Phase.

Arm type	Experimental
Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 10 mg, orally

Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 20 mg, orally

Arm title	DB Phase: AZM-H 10 mg + 40 mg/ 80 mg

Arm description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive High-Dose Azilsartan Medoxomil (AZM-H) in the DB Phase. Participants with body weight >=25 to <50 kg received AZM-H orally, once daily 10 mg from Weeks 0-2 and AZM-H 40 mg from Weeks 2-6 and participants with body weight >=50 kg received AZM-H orally, once daily 10 mg from Weeks 0-2 and AZM-H 80 mg from Weeks 2-6 in the DB Phase.

Arm type	Experimental
Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 10 mg, orally

Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: AZM tablets, 80 mg, orally	
Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
AZM tablets, 40 mg, orally

Number of subjects in period 1	DB Phase: Losartan 25 mg + 50 mg + 100 mg	DB Phase: Low-Dose Azilsartan Medoxomil (AZM-L) 10 mg	DB Phase: AZM-M 10 mg+20 mg
Started	53	52	56
Completed	47	52	53
Not completed	6	0	3
Pretreatment Event/Adverse Event	1	-	1
Major Protocol Deviation	1	-	-
Voluntary Withdrawal	2	-	2
Lost to follow-up	1	-	-
Reason not Specified	1	-	-

Number of subjects in period 1	DB Phase: AZM-H 10 mg + 40 mg/ 80 mg
Started	54
Completed	51
Not completed	3
Pretreatment Event/Adverse Event	-
Major Protocol Deviation	1
Voluntary Withdrawal	2
Lost to follow-up	-
Reason not Specified	-

Period 2

Period 2 title	Withdrawal Phase (From Weeks 6 to 8)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	WD Phase: Pooled Placebo

Arm description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive placebo in WD Phase, orally, once daily from Week 6-8. Pooled placebo included all participants who were on AZM or losartan in DB period and switched to placebo in WD Phase.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet, orally

Arm title	WD Phase: Losartan 100 mg + 50 mg

Arm description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive losartan in WD Phase. Participants with body weight >=25 to <50 kg received losartan 50 mg orally, once daily from Weeks 6-8 or participants with body weight >=50 kg received losartan 100 mg orally, once daily from Weeks 6-8 in WD Phase.

Arm type	Active comparator
Investigational medicinal product name	Losartan potassium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Losartan over encapsulated tablets, 50 mg, orally

Investigational medicinal product name	Losartan potassium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Losartan over encapsulated tablets, 100 mg, orally

Arm title	WD Phase: AZM-L 10 mg

Arm description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to AZM-L in WD Phase. Participants with body weight >=25 to <50 kg or >=50 kg received AZM-L 10 mg orally, once daily from Weeks 6-8 in WD Phase.

Arm type	Experimental
Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 10 mg, orally

Arm title	WD Phase: AZM-M 20 mg

Arm description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to

receive AZM-M in WB Phase. Participants with body weight >=25 to <50 kg or >=50 kg received AZM-M 20 mg orally, once daily from Weeks 6-8 WD Phase.

Arm type	Experimental
Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 20 mg, orally

Arm title	WD Phase: AZM-H 40 mg + 80 mg

Arm description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive AZM-H in WD Phase. Participants with body weight >=25 to <50 kg received AZM-M 40 mg orally, once daily from Weeks 6-8 or participants with body weight >=50 kg received AZM-M 80 mg orally, once daily from Weeks 6-8 in WD Phase.

Arm type	Experimental
Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 40 mg, orally

Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 80 mg, orally

Number of subjects in period 2	WD Phase: Pooled Placebo	WD Phase: Losartan 100 mg + 50 mg	WD Phase: AZM-L 10 mg
Started	103	23	26
Completed	103	23	26
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

Number of subjects in period 2	WD Phase: AZM-M 20 mg	WD Phase: AZM-H 40 mg + 80 mg
Started	26	25
Completed	25	25
Not completed	1	0
Consent withdrawn by subject	1	-

Period 3

Period 3 title	Open-Label Phase (From Weeks 8 to 52)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	OL Phase: AZM Only 10 mg + 20 mg + 40 mg/ 80 mg

Arm description:

Following the WD Phase, participants who had primary and secondary hypertension were randomized to AZM only Open-label Phase. Participants with body weight >=25 to <50 kg received AZM 10 mg orally, once daily from Weeks 8-12 and 20 or 40 mg from Weeks 12-52 or Participants with body weight >=50 kg received AZM 10 mg orally, once daily from Weeks 8-12 and 10, 20, 40, or 80 mg AZM orally, once daily from Weeks 12-52 in Open-label Phase.

Arm type	Experimental
Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 10 mg orally

Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 20 mg orally

Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 40 mg orally

Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 80 mg orally

Arm title	OL Phase: AZM Plus [AZM + Other Antihypertensives]

Arm description:

Following the WD Phase, participants who had primary and secondary hypertension were randomized to AZM Plus in Open-label Phase. Participants with body weight >=25 to <50 kg received AZM 10 mg orally, once daily from Weeks 8-12 and 10, 20, or 40 mg AZM orally, once daily from Weeks 12-52 or body weight ≥50 kg received AZM 10 mg orally, once daily from Weeks 8-12 and 10, 20, 40, or 80 mg AZM orally, once daily from Weeks 12-52 plus other antihypertensive medications as needed according to a titrate-to-target algorithm, antihypertensive medication in Open-label Phase.

Arm type	Experimental

Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 10 mg orally

Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 40 mg orally

Investigational medicinal product name	Azilsartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZM tablets, 80 mg orally

Investigational medicinal product name	Antihypertensive Agents (a calcium channel blocker - amlodipine; a diuretic - hydrochlorothiazide, or a beta-blocker - metoprolol)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Antihypertensive tablet, orally

Number of subjects in period 3[1]	OL Phase: AZM Only 10 mg + 20 mg + 40 mg/ 80 mg	OL Phase: AZM Plus [AZM + Other Antihypertensives]
Started	156	41
Completed	140	41
Not completed	16	0
Consent withdrawn by subject	7	-
Study Termination	1	-
Pregnancy	1	-
Lost to follow-up	2	-
Reason not Specified	5	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all participants who completed previous period, entered the preceding period.

Baseline characteristics

Reporting groups	
Reporting group title	DB Phase: Losartan 25 mg + 50 mg + 100 mg
Reporting group description:	
Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive the losartan in the DB Phase. Participants with body weight >=25 to <50 kg were randomized to receive losartan 25 mg orally once daily, from Weeks 0 to 2 and losartan 50 mg from Weeks 2 to 6 and participants with body weight >=50 kg received losartan orally once daily 50 mg, from Weeks 0 to 2 and losartan 100 mg from Weeks 2 to 6 in the DB Phase.	
Reporting group title	DB Phase: Low-Dose Azilsartan Medoxomil (AZM-L) 10 mg
Reporting group description:	
Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive the low-dose AZM-L DB Phase. Participants with body weight >= 25 to <50 kg or >= 50 kg received AZM-L 10 mg, orally, once daily from Week 0-6 in the DB Phase.	
Reporting group title	DB Phase: AZM-M 10 mg+20 mg
Reporting group description:	
Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive Intermediate-Dose Azilsartan Medoxomil (AZM-M) in the DB Phase. Participants with body weight >=25 to <50 kg or >=50 kg received AZM-M orally, once daily 10 mg from Weeks 0-2 and AZM-M 20 mg from Weeks 2-6 in the DB Phase.	
Reporting group title	DB Phase: AZM-H 10 mg + 40 mg/ 80 mg
Reporting group description:	
Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive High-Dose Azilsartan Medoxomil (AZM-H) in the DB Phase. Participants with body weight >=25 to <50 kg received AZM-H orally, once daily 10 mg from Weeks 0-2 and AZM-H 40 mg from Weeks 2-6 and participants with body weight >=50 kg received AZM-H orally, once daily 10 mg from Weeks 0-2 and AZM-H 80 mg from Weeks 2-6 in the DB Phase.	

Reporting group values	DB Phase: Losartan 25 mg + 50 mg + 100 mg	DB Phase: Low-Dose Azilsartan Medoxomil (AZM-L) 10 mg	DB Phase: AZM-M 10 mg+20 mg
Number of subjects	53	52	56
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	13.2	13.4	13.4
standard deviation	± 3.18	± 2.92	± 3.10
Gender Categorical Units: Subjects			
Female	25	28	16
Male	28	24	40
Ethnicity Units: Subjects			
Hispanic or Latino	17	13	12
Non-Hispanic or Latino	36	39	44
Race Units: Subjects			
American Indian or Alaskan Native	1	1	0
Black or African American	13	13	14
White	38	38	42

Multiracial	1	0	0

Height			
Units: cm			
arithmetic mean	159.4	159.0	160.3
standard deviation	± 15.51	± 15.11	± 17.43
Body Mass Index (BMI)			
BMI=weight (kg)/[height (m)^2]			
Units: kg/m^2			
arithmetic mean	26.35	27.98	25.41
standard deviation	± 7.466	± 8.360	± 6.977
Weight			
Units: kg			
arithmetic mean	69.00	72.53	66.65
standard deviation	± 26.235	± 28.556	± 24.627

Reporting group values	DB Phase: AZM-H 10 mg + 40 mg/ 80 mg	Total	
Number of subjects	54	215	
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	13.5		
standard deviation	± 2.85	-	
Gender Categorical			
Units: Subjects			
Female	25	94	
Male	29	121	
Ethnicity			
Units: Subjects			
Hispanic or Latino	8	50	
Non-Hispanic or Latino	46	165	
Race			
Units: Subjects			
American Indian or Alaskan Native	1	3	
Black or African American	15	55	
White	37	155	
Multiracial	1	2	
Height			
Units: cm			
arithmetic mean	158.9		
standard deviation	± 14.67	-	
Body Mass Index (BMI)			
BMI=weight (kg)/[height (m)^2]			
Units: kg/m^2			
arithmetic mean	26.75		
standard deviation	± 7.309	-	
Weight			

Units: kg			
arithmetic mean	68.94		
standard deviation	± 24.744	-	

End points reporting groups

Reporting group title	DB Phase: Losartan 25 mg + 50 mg + 100 mg

Reporting group description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive the losartan in the DB Phase. Participants with body weight >=25 to <50 kg were randomized to receive losartan 25 mg orally once daily, from Weeks 0 to 2 and losartan 50 mg from Weeks 2 to 6 and participants with body weight >=50 kg received losartan orally once daily 50 mg, from Weeks 0 to 2 and losartan 100 mg from Weeks 2 to 6 in the DB Phase.

Reporting group title	DB Phase: Low-Dose Azilsartan Medoxomil (AZM-L) 10 mg

Reporting group description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive the low-dose AZM-L DB Phase. Participants with body weight >= 25 to <50 kg or >= 50 kg received AZM-L 10 mg, orally, once daily from Week 0-6 in the DB Phase.

Reporting group title	DB Phase: AZM-M 10 mg+20 mg

Reporting group description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive Intermediate-Dose Azilsartan Medoxomil (AZM-M) in the DB Phase. Participants with body weight >=25 to <50 kg or >=50 kg received AZM-M orally, once daily 10 mg from Weeks 0-2 and AZM-M 20 mg from Weeks 2-6 in the DB Phase.

Reporting group title	DB Phase: AZM-H 10 mg + 40 mg/ 80 mg

Reporting group description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive High-Dose Azilsartan Medoxomil (AZM-H) in the DB Phase. Participants with body weight >=25 to <50 kg received AZM-H orally, once daily 10 mg from Weeks 0-2 and AZM-H 40 mg from Weeks 2-6 and participants with body weight >=50 kg received AZM-H orally, once daily 10 mg from Weeks 0-2 and AZM-H 80 mg from Weeks 2-6 in the DB Phase.

Reporting group title	WD Phase: Pooled Placebo

Reporting group description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive placebo in WD Phase, orally, once daily from Week 6-8. Pooled placebo included all participants who were on AZM or losartan in DB period and switched to placebo in WD Phase.

Reporting group title	WD Phase: Losartan 100 mg + 50 mg

Reporting group description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive losartan in WD Phase. Participants with body weight >=25 to <50 kg received losartan 50 mg orally, once daily from Weeks 6-8 or participants with body weight >=50 kg received losartan 100 mg orally, once daily from Weeks 6-8 in WD Phase.

Reporting group title	WD Phase: AZM-L 10 mg

Reporting group description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to AZM-L in WD Phase. Participants with body weight >=25 to <50 kg or >=50 kg received AZM-L 10 mg orally, once daily from Weeks 6-8 in WD Phase.

Reporting group title	WD Phase: AZM-M 20 mg

Reporting group description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive AZM-M in WB Phase. Participants with body weight >=25 to <50 kg or >=50 kg received AZM-M 20 mg orally, once daily from Weeks 6-8 WD Phase.

Reporting group title	WD Phase: AZM-H 40 mg + 80 mg

Reporting group description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive AZM-H in WD Phase. Participants with body weight >=25 to <50 kg received AZM-M 40 mg orally, once daily from Weeks 6-8 or participants with body weight >=50 kg received AZM-M 80 mg orally, once daily from Weeks 6-8 in WD Phase.

Reporting group title	OL Phase: AZM Only 10 mg + 20 mg + 40 mg/ 80 mg

Reporting group description:

Following the WD Phase, participants who had primary and secondary hypertension were randomized to

AZM only Open-label Phase. Participants with body weight >=25 to <50 kg received AZM 10 mg orally, once daily from Weeks 8-12 and 20 or 40 mg from Weeks 12-52 or Participants with body weight >=50 kg received AZM 10 mg orally, once daily from Weeks 8-12 and 10, 20, 40, or 80 mg AZM orally, once daily from Weeks 12-52 in Open-label Phase.

Reporting group title	OL Phase: AZM Plus [AZM + Other Antihypertensives]

Reporting group description:

Following the WD Phase, participants who had primary and secondary hypertension were randomized to AZM Plus in Open-label Phase. Participants with body weight >=25 to <50 kg received AZM 10 mg orally, once daily from Weeks 8-12 and 10, 20, or 40 mg AZM orally, once daily from Weeks 12-52 or body weight ≥50 kg received AZM 10 mg orally, once daily from Weeks 8-12 and 10, 20, 40, or 80 mg AZM orally, once daily from Weeks 12-52 plus other antihypertensive medications as needed according to a titrate-to-target algorithm, antihypertensive medication in Open-label Phase.

Subject analysis set title	WD Phase: Pooled AZM
Subject analysis set type	Full analysis

Subject analysis set description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive AZM in WD Phase. Participants received AZM-L 10 mg, AZM – M 20 mg, and AZM – H 40 mg/80 mg orally, once daily from Weeks 6-8 based on their body weight. Data for all participants were pooled for analysis and is reported together in this arm.

Subject analysis set title	DB Phase: Pooled AZM
Subject analysis set type	Full analysis

Subject analysis set description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive the AZM in the DB phase. Participants received AZM-L 10 mg from Week 0-6, AZM-M and AZM-L 10 mg from Weeks 0-2, AZM-M 20 mg, and AZM-H 40 mg/80 mg from Weeks 2-6 orally, once daily based on their body weight. Data for all participants were pooled for analysis and is reported together in this arm.

Subject analysis set title	OL Phase: Pooled AZM
Subject analysis set type	Safety analysis

Subject analysis set description:

Following the WD Phase, participants who had primary and secondary hypertension were randomized to receive AZM in Open-label Phase. Participants received AZM-L 10 mg from Weeks 8-12, AZM-M and AZM-L 10 mg, AZM-M 20 mg, and AZM-H 40 mg/80 mg from Weeks 12-52 orally, once daily based on their body weight. Data for all participants were pooled for analysis and is reported together in this arm.

Primary: Change From Week 6 (Final Visit) of the Double-Blind Phase to Week 8 (Final Visit) of the Withdrawal Phase in Trough Clinic Seated Diastolic Blood Pressure (SeDBP)

End point title	Change From Week 6 (Final Visit) of the Double-Blind Phase to Week 8 (Final Visit) of the Withdrawal Phase in Trough Clinic Seated Diastolic Blood Pressure (SeDBP)

End point description:

The change in trough clinic seDBP measured From Week 6 (Final Visit) of the DB Phase to Week 8 (Final Visit) of the WD Phase. The trough is the average of the non-missing values of 3 serial trough sitting DBP measurements. Blood pressure was measured using a validated, automated device after the participant had been sitting for at least 5 minutes. Week 6 to Week 8 blood pressure was measured approximately 24 hours after the previous day's dose. The primary endpoint compared the change in SeDBP in Pooled AZM versus Pooled Placebo arm. Full Analysis Set included all randomized participants who had received at least one dose of double-blind study medication for the respective study phase. ‘n’ indicates the number of participants with data available at the given time-point.

End point type	Primary

End point timeframe:

Week 6 (Final Visit) of the DB phase to Week 8 (Final Visit) of the WD phase

End point values	WD Phase: Pooled Placebo	WD Phase: Pooled AZM		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	79	77		
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Week 6 (n= 79,77)	74.2 (± 8.43)	74.6 (± 8.77)		
Change From Weeks 6 to 8 (n= 79,76)	3.9 (± 8.00)	-1.6 (± 6.69)		

Statistical analyses

Statistical analysis title	Pooled AZM vs Pooled Placebo
Comparison groups	WD Phase: Pooled Placebo v WD Phase: Pooled AZM
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-5.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.29
upper limit	-3.55
Variability estimate	Standard error of the mean
Dispersion value	0.956

Notes:

[1] - Comparisons between pooled AZM dose to pooled placebo were done from framework of analysis of covariance (ANCOVA) using contrast statements from within sequential testing procedure of successful conclusion of statistical significance.

Secondary: Change From Week 6 (Final Visit) of the Double-Blind Phase to Week 8 (Final Visit) of the Withdrawal Phase in Trough Clinic Seated Systolic Blood Pressure (SeSBP)

End point title	Change From Week 6 (Final Visit) of the Double-Blind Phase to Week 8 (Final Visit) of the Withdrawal Phase in Trough Clinic Seated Systolic Blood Pressure (SeSBP)

End point description:

The change in trough clinic seSBP measured From Week 6 (Final Visit) of the DB Phase to Week 8 (Final Visit) of the WD Phase. The trough is the average of the non-missing values of 3 serial trough seSBP measurements. Blood pressure was measured using a validated, automated device after the participant had been sitting for at least 5 minutes. Week 6 to Week 8 blood pressure was measured approximately 24 hours after the previous day's dose. This secondary endpoint compared the change in Trough SeSBP in Pooled AZM versus Pooled Placebo arm. FAS included all randomized participants who had received at least one dose of double-blind study medication for the respective study phase. 'n' indicates the number of participants with data available at the given time-point.

End point type	Secondary

End point timeframe:

Week 6 (Final Visit) of the DB phase to Week 8 (Final Visit) of the WD

End point values	WD Phase: Pooled Placebo	WD Phase: Pooled AZM		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	79	77		
Units: mmHg				
arithmetic mean (standard deviation)				
Week 6 (n=79, 77)	122.5 (± 13.65)	122.2 (± 13.18)		
Change from Weeks 6 to 8 (n=79, 76)	4.4 (± 9.96)	-2.3 (± 8.72)		

Statistical analyses

Statistical analysis title	Pooled AZM Vs Pooled Placebo
Comparison groups	WD Phase: Pooled Placebo v WD Phase: Pooled AZM
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-7.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.67
upper limit	-4.41
Variability estimate	Standard error of the mean
Dispersion value	1.34

Notes:

[2] - Comparisons between Pooled AZM dose to Pooled Placebo were done from the framework of the above ANCOVA using contrast statements. The p-value indicates significance at the 5% level.

Secondary: Change From Week 6 (Final Visit) of the Double-Blind Phase to Week 8 (Final Visit) of the Withdrawal Phase in Mean Arterial Pressure (MAP)

End point title	Change From Week 6 (Final Visit) of the Double-Blind Phase to Week 8 (Final Visit) of the Withdrawal Phase in Mean Arterial Pressure (MAP)

End point description:

MAP was calculated using formula: MAP= seSBP +2 (seDBP)/3. Blood pressure was measured using a validated, automated device after the participant had been sitting for at least 5 minutes. Week 6 to Week 8 blood pressure was measured approximately 24 hours after the previous day's dose. This secondary endpoint compared the MAP in pooled AZM versus pooled placebo. FAS included all randomized participants who had received at least one dose of double-blind study medication for the respective study phase. 'n' indicates the number of participants with data available at the given time-point.

End point type	Secondary

End point timeframe:

Week 6 (Final Visit) of the DB Phase to Week 8 (Final Visit) of the WD Phase

End point values	WD Phase: Pooled Placebo	WD Phase: Pooled AZM		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	79	77		
Units: mmHg				
arithmetic mean (standard deviation)				
Week 6 (n=79, 77)	90.3 (± 9.25)	90.5 (± 9.41)		
Change from Weeks 6 to 8 (n=79, 76)	4.1 (± 7.43)	-1.8 (± 6.63)		

Statistical analyses

Statistical analysis title	Pooled AZM Vs Pooled Placebo
Comparison groups	WD Phase: Pooled Placebo v WD Phase: Pooled AZM
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-5.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.86
upper limit	-4.11
Variability estimate	Standard error of the mean
Dispersion value	0.957

Notes:

[3] - Comparisons between Pooled AZM dose to Pooled Placebo were done from framework of ANCOVA using contrast statements from within sequential testing procedure of successful statistical significance. P-value indicates significance at 5% level.

Secondary: Change From Baseline in Trough Clinic seDBP at Week 6 (Final Visit)

End point title	Change From Baseline in Trough Clinic seDBP at Week 6 (Final Visit)[4]

End point description:

The change in trough clinic seDBP measured at Week 6 relative to Baseline. The trough is the average of the non-missing value of serial trough seDBP measurements. Blood pressure was measured using a validated, automated device after the participant had been sitting for at least 5 minutes. Week 6 blood pressure was measured approximately 24 hours after the previous day's dose. This secondary endpoint compared the seDBP at Week 6 in pooled AZM versus losartan. FAS included all randomized participants who had received at least one dose of DB study medication for the respective study phase. 'n' indicates the number of participants with data available at the given time-point.

End point type	Secondary

End point timeframe:

Baseline to Week 6 (Final Visit) of the DB Phase

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data was reported for the pooled analyses in all the endpoints.

End point values	DB Phase: Losartan 25 mg + 50 mg + 100 mg	DB Phase: Pooled AZM		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	53	162		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (n=53, 162)	87.6 (± 6.93)	85.9 (± 5.68)		
Change from Baseline to Week 6 (n=47, 156)	-9.5 (± 8.10)	-11.6 (± 8.71)		

Statistical analyses

Statistical analysis title	Pooled AZM vs Losartan
Comparison groups	DB Phase: Losartan 25 mg + 50 mg + 100 mg v DB Phase: Pooled AZM
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [5]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.17
upper limit	-0.78
Variability estimate	Standard error of the mean
Dispersion value	1.366

Notes:

[5] - Comparisons between each AZM dose to losartan were done from the framework of the above MMRM. The p-value indicates significance at the 5% level.

Secondary: Change From Baseline in Trough Clinic seSBP at Week 6 (Final Visit)

End point title	Change From Baseline in Trough Clinic seSBP at Week 6 (Final Visit)[6]

End point description:

The change in trough clinic seSBP measured at Week 6 relative to Baseline. The trough is the average of the non-missing values of serial trough seSBP measurements. Blood pressure was measured using a validated, automated device after the participant had been sitting for at least 5 minutes. Week 6 blood pressure was measured approximately 24 hours after the previous day's dose. This secondary endpoint compared the seSBP in pooled AZM versus losartan. FAS included all randomized participants who had received at least one dose of DB study medication for the respective study phase. 'n' indicates the number of participants with data available at the given time-point.

End point type	Secondary

End point timeframe:

Baseline to Week 6 (Final Visit) of the DB Phase

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was reported for the pooled analyses in all the endpoints.

End point values	DB Phase: Losartan 25 mg + 50 mg + 100 mg	DB Phase: Pooled AZM		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	53	162		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (n=53, 162)	134.3 (± 9.68)	132.3 (± 10.42)		
Change from Baseline to Week 6 (n=47, 156)	-10.0 (± 11.57)	-10.0 (± 9.48)		

Statistical analyses

Statistical analysis title	Pooled AZM Vs Losartan
Comparison groups	DB Phase: Losartan 25 mg + 50 mg + 100 mg v DB Phase: Pooled AZM
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.547 [7]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.23
upper limit	2.25
Variability estimate	Standard error of the mean
Dispersion value	1.642

Notes:

[7] - Comparisons between each AZM dose to losartan were done from the framework of the above MMRM.

Secondary: Change From Baseline in Trough Clinic MAP at Week 6 (Final Visit)

End point title	Change From Baseline in Trough Clinic MAP at Week 6 (Final Visit)[8]

End point description:

The change in trough clinic MAP measured at Week 6 relative to Baseline. The trough is the average of the non-missing value of serial trough MAP measurements. MAP was calculated using formula: MAP= seSBP +2 (seDBP)/3. Blood pressure was measured using a validated, automated device after the participant had been sitting for at least 5 minutes. MAP was measured approximately 24 hours after the previous day's dose. This secondary endpoint compared the MAP in pooled AZM versus Losartan.Full Analysis Set included all randomized participants who had received at least one dose of DB study medication for the respective study phase. ‘n’ indicates the number of participants with data available at the given time-point.

End point type	Secondary

End point timeframe:

Baseline to Week 6 (Final Visit) of the DB phase

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was reported for the pooled analyses in all the endpoints.

End point values	DB Phase: Losartan 25 mg + 50 mg + 100 mg	DB Phase: Pooled AZM		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	53	162		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (n=53, 162)	103.1 (± 7.19)	101.4 (± 6.41)		
Change from Baseline to Week 6 (47, 156)	-9.6 (± 8.66)	-11.1 (± 7.93)		

Statistical analyses

Statistical analysis title	Pooled AZM Vs Losartan
Comparison groups	DB Phase: Losartan 25 mg + 50 mg + 100 mg v DB Phase: Pooled AZM
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.062 [9]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.15
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	1.337

Notes:

[9] - Comparisons between each AZM dose to losartan were done from the framework of the above MMRM.

Secondary: Percentage of Participants who Achieved Target Blood Pressure (BP) (SeDBP, SeSBP, both) at Week 8 (Final Visit) of the Withdrawal Phase, With the Target Defined as <90th Percentile for Age, Gender, and Height

End point title	Percentage of Participants who Achieved Target Blood Pressure (BP) (SeDBP, SeSBP, both) at Week 8 (Final Visit) of the Withdrawal Phase, With the Target Defined as <90th Percentile for Age, Gender, and Height

End point description:

Clinic seDBP, seSBP both (seDBP, and seSBP) target defined as <90th Percentile for age, gender, and height. Blood pressure was measured using a validated, automated device after the participant had been sitting for at least 5 minutes. Week 8 blood pressure was measured approximately 24 hours after the previous day's dose. This secondary endpoint compared the SeDBP, SeSBP, both in pooled AZM versus pooled placebo. Full Analysis Set included all randomized participants who had received at least one dose of DB study medication for the respective study phase. The analysis was based on last

observation carried forward (LOCF).

End point type	Secondary

End point timeframe:

Week 8 (Final Visit) of the WD Phase

End point values	WD Phase: Pooled Placebo	WD Phase: Pooled AZM		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	79	77		
Units: percentage of participants				
number (not applicable)				
Achieved Target seDBP	50.6	66.2		
Achieved Target seSBP	39.2	61.0		
Achieved Both (Target seDBP and seSBP)	30.4	54.5		

Statistical analyses

Statistical analysis title	SeDBP: Pooled AZM vs Pooled Placebo
Comparison groups	WD Phase: Pooled Placebo v WD Phase: Pooled AZM
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028 [10]
Method	Logistic Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	4.43

Notes:

[10] - The p-values and odds ratios were obtained using a logistic model with treatment, age, race, and weight as
fixed effects and corresponding baseline clinic BP as a covariate. The p-value indicated significance at the 5% level.

Statistical analysis title	SeSBP: Pooled AZM Vs Pooled Placebo
Comparison groups	WD Phase: Pooled Placebo v WD Phase: Pooled AZM
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [11]
Method	Logistic Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	4.76

Notes:

[11] - The p-values and odds ratios were obtained using a logistic model with treatment, age, race, and weight as
fixed effects and corresponding baseline clinic BP as a covariate.

Statistical analysis title	Both: Pooled AZM Vs Pooled Placebo
Comparison groups	WD Phase: Pooled Placebo v WD Phase: Pooled AZM
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [12]
Method	Logistic Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.36
upper limit	5.77

Notes:

[12] - The p-values and odds ratios were obtained using a logistic model with treatment, age, race, and weight as
fixed effects and corresponding baseline clinic BP as a covariate. The p-value indicated significance at the 1% level.

Secondary: Percentage of Participants with At least One Treatment-Emergent Adverse Event (TEAE)

End point title	Percentage of Participants with At least One Treatment-Emergent Adverse Event (TEAE)[13]

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. TEAE is defined as any AE that started or worsened on or after the start of the study medication and after the discontinuation of the study medication.

End point type	Secondary

End point timeframe:

From the time of the first dose of study drug through 30 days after the last dose (Up to 54 weeks)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was reported for the pooled analyses in all the endpoints.

End point values	DB Phase: Losartan 25 mg + 50 mg + 100 mg	WD Phase: Pooled Placebo	WD Phase: Losartan 100 mg + 50 mg	WD Phase: Pooled AZM
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	53	103	23	77
Units: percentage of participants				
number (not applicable)	32.1	12.6	8.7	15.6

End point values	DB Phase: Pooled AZM	OL Phase: Pooled AZM		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	162	197		
Units: percentage of participants				
number (not applicable)	33.3	43.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of the first dose of study drug through 30 days after the last dose (Up to 54 weeks)

Adverse event reporting 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. Data for adverse events are reported for each phase of the study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	OL Phase: Pooled AZM

Reporting group description:

Following the WD Phase, participants who had primary and secondary hypertension were randomized to receive AZM in Open-label Phase. Participants received AZM-L 10 mg from Week 8-12, AZM-M and AZM-L 10 mg, AZM-M 20 mg, and AZM-H 40 mg/ 80 mg from Week 12-52 orally, once daily based on their body weight. Data for all participants were pooled for analysis and is reported together in this arm.

Reporting group title	DB Phase: Pooled AZM

Reporting group description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive the AZM in the DB phase. Participants received AZM-L 10 mg from Week 0-6, AZM-M and AZM-L 10 mg from Week 0-2, AZM-M 20 mg, and AZM-H 40 mg/ 80 mg from Week 2-6 orally, once daily based on their body weight. Data for all participants were pooled for analysis and is reported together in this arm.

Reporting group title	WD Phase: Pooled Placebo

Reporting group description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive placebo in WD Phase, orally, once daily from Week 6-8. Pooled placebo included all participants who were on AZM or losartan in DB period and switched to placebo in WD Phase.

Reporting group title	WD Phase: Losartan

Reporting group description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive losartan in WD Phase. Participants with body weight >=25 to <50 kg received losartan 50 mg orally, once daily from Weeks 6-8 or participants with body weight >=50 kg received losartan 100 mg orally, once daily from Weeks 6-8 in WD Phase.

Reporting group title	DB Phase: Losartan

Reporting group description:

Following the Placebo Run-in Period, participants who had primary or secondary hypertension were randomized to receive the losartan in the DB Phase. Participants with body weight >=25 to <50 kg were randomized to receive losartan 25 mg orally once daily, from Weeks 0 to 2 and losartan 50 mg from Weeks 2 to 6 and participants with body weight >=50 kg received losartan orally once daily 50 mg, from Weeks 0 to 2 and losartan 100 mg from Weeks 2 to 6 in the DB Phase.

Reporting group title	WD Phase: Pooled AZM

Reporting group description:

Following the DB Phase, participants who had primary or secondary hypertension were randomized to receive AZM in WD Phase. Participants received AZM-L 10 mg, AZM – M 20 mg, and AZM – H 40 mg/ 80 mg orally, once daily from Week 6-8 based on their body weight. Data for all participants were pooled for analysis and is reported together in this arm.

Serious adverse events	OL Phase: Pooled AZM	DB Phase: Pooled AZM	WD Phase: Pooled Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 197 (4.57%)	2 / 162 (1.23%)	0 / 103 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 197 (0.00%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 197 (0.00%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Transplant rejection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Autism spectrum disorder			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 197 (0.51%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	WD Phase: Losartan	DB Phase: Losartan	WD Phase: Pooled AZM
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	1 / 77 (1.30%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Blood pressure increased			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Transplant rejection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Autism spectrum disorder			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Upper respiratory tract infection			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	OL Phase: Pooled AZM	DB Phase: Pooled AZM	WD Phase: Pooled Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 197 (42.64%)	53 / 162 (32.72%)	13 / 103 (12.62%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 197 (1.52%)	0 / 162 (0.00%)	1 / 103 (0.97%)
occurrences (all)	3	0	1
Hypotension			
subjects affected / exposed	2 / 197 (1.02%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	2	1	0
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	4 / 197 (2.03%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	4	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Seasonal allergy			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Vaginal discharge			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Polycystic ovaries			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Bronchospasm			
subjects affected / exposed	0 / 197 (0.00%)	0 / 162 (0.00%)	1 / 103 (0.97%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	3 / 197 (1.52%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	3	1	0

Bronchial hyperreactivity			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	4 / 197 (2.03%)	0 / 162 (0.00%)	1 / 103 (0.97%)
occurrences (all)	4	0	1
Oropharyngeal pain			
subjects affected / exposed	6 / 197 (3.05%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	6	1	0
Respiratory tract congestion			
subjects affected / exposed	0 / 197 (0.00%)	0 / 162 (0.00%)	1 / 103 (0.97%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	2 / 197 (1.02%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	2	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Nervousness			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 197 (0.51%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	1	1	0
Arthroscopy			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			

subjects affected / exposed	2 / 197 (1.02%)	2 / 162 (1.23%)	0 / 103 (0.00%)
occurrences (all)	2	2	0
Blood creatinine increased			
subjects affected / exposed	1 / 197 (0.51%)	3 / 162 (1.85%)	0 / 103 (0.00%)
occurrences (all)	1	3	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	2 / 197 (1.02%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	2	1	0
Cardiac murmur			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	1 / 103 (0.97%)
occurrences (all)	1	0	1
Blood glucose decreased			
subjects affected / exposed	0 / 197 (0.00%)	2 / 162 (1.23%)	1 / 103 (0.97%)
occurrences (all)	0	2	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 197 (0.00%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Influenza B virus test positive			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	3 / 197 (1.52%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	3	0	0
Ligament injury			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Foot fracture			
subjects affected / exposed	2 / 197 (1.02%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	2	0	0
Joint dislocation			
subjects affected / exposed	2 / 197 (1.02%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	2	0	0
Fibula fracture			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Upper limb fracture			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Soft tissue injury			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	4 / 197 (2.03%)	5 / 162 (3.09%)	0 / 103 (0.00%)
occurrences (all)	4	5	0
Headache			
subjects affected / exposed	17 / 197 (8.63%)	8 / 162 (4.94%)	6 / 103 (5.83%)
occurrences (all)	17	8	6
Hypoaesthesia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Migraine			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 197 (0.00%)	2 / 162 (1.23%)	0 / 103 (0.00%)
occurrences (all)	0	2	0
Syncope			
subjects affected / exposed	1 / 197 (0.51%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	1	1	0
Presyncope			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 197 (0.51%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	1	1	0
Neutropenia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Lymphadenitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Middle ear inflammation			
subjects affected / exposed	0 / 197 (0.00%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 197 (0.00%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Blindness			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis allergic			
subjects affected / exposed	3 / 197 (1.52%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 197 (3.55%)	1 / 162 (0.62%)	2 / 103 (1.94%)
occurrences (all)	7	1	2
Enteritis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	8 / 197 (4.06%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	8	1	0
Constipation			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	4 / 197 (2.03%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	4	1	0
Odynophagia			

subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Salivary gland pain			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	6 / 197 (3.05%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	6	0	0
Gastritis			
subjects affected / exposed	1 / 197 (0.51%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	1	1	0
Food poisoning			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 197 (0.00%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	2 / 197 (1.02%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	2	1	0
Vomiting			
subjects affected / exposed	4 / 197 (2.03%)	2 / 162 (1.23%)	0 / 103 (0.00%)
occurrences (all)	4	2	0
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	2 / 197 (1.02%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	2	0	0
Acne			

subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Dermatitis atopic			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Nail bed inflammation			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Skin exfoliation			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 197 (0.00%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	2 / 197 (1.02%)	1 / 162 (0.62%)	1 / 103 (0.97%)
occurrences (all)	2	1	1
Pruritus allergic			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Thyroid cyst			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 197 (1.02%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	2	0	0
Back pain			

subjects affected / exposed	2 / 197 (1.02%)	4 / 162 (2.47%)	1 / 103 (0.97%)
occurrences (all)	2	4	1
Intervertebral disc protrusion			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	3 / 197 (1.52%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	3	1	0
Myositis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 197 (0.51%)	2 / 162 (1.23%)	0 / 103 (0.00%)
occurrences (all)	1	2	0
Bacteraemia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	3 / 197 (1.52%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	3	1	0
Cystitis			
subjects affected / exposed	2 / 197 (1.02%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	2	0	0
Dental fistula			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Dermatophytosis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0

Gastrointestinal viral infection			
subjects affected / exposed	2 / 197 (1.02%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis viral			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	5 / 197 (2.54%)	4 / 162 (2.47%)	1 / 103 (0.97%)
occurrences (all)	5	4	1
Herpangina			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	4 / 197 (2.03%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	4	0	0
Nasopharyngitis			
subjects affected / exposed	8 / 197 (4.06%)	5 / 162 (3.09%)	1 / 103 (0.97%)
occurrences (all)	8	5	1
Otitis externa			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Otitis media acute			
subjects affected / exposed	1 / 197 (0.51%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	1	1	0
Pharyngitis			
subjects affected / exposed	7 / 197 (3.55%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	7	1	0
Respiratory tract infection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0

Pneumonia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	1 / 103 (0.97%)
occurrences (all)	1	0	1
Pharyngotonsillitis			
subjects affected / exposed	3 / 197 (1.52%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	3	1	0
Rhinitis			
subjects affected / exposed	2 / 197 (1.02%)	2 / 162 (1.23%)	0 / 103 (0.00%)
occurrences (all)	2	2	0
Viral pharyngitis			
subjects affected / exposed	2 / 197 (1.02%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	2	0	0
Sinusitis			
subjects affected / exposed	3 / 197 (1.52%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	3	0	0
Tonsillitis			
subjects affected / exposed	3 / 197 (1.52%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	3	0	0
Appendicitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	8 / 197 (4.06%)	8 / 162 (4.94%)	0 / 103 (0.00%)
occurrences (all)	8	8	0
Tracheobronchitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	5 / 197 (2.54%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	5	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 197 (1.52%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	3	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0

Urinary tract infection			
subjects affected / exposed	1 / 197 (0.51%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	1	1	0
Varicella			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	3 / 197 (1.52%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	3	0	0
Dyslipidaemia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 162 (0.62%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Obesity			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 197 (0.00%)	2 / 162 (1.23%)	0 / 103 (0.00%)
occurrences (all)	0	2	0
Insulin resistance			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Lipid metabolism disorder			
subjects affected / exposed	1 / 197 (0.51%)	0 / 162 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	WD Phase: Losartan	DB Phase: Losartan	WD Phase: Pooled AZM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 23 (8.70%)	15 / 53 (28.30%)	11 / 77 (14.29%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Vaginal discharge			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Polycystic ovaries			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Bronchospasm			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Cough			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Bronchial hyperreactivity			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Nervousness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Arthroscopy			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Blood glucose decreased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Influenza B virus test positive			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Ligament injury			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Joint dislocation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Fibula fracture			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Upper limb fracture			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Soft tissue injury			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Tooth fracture			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	3 / 77 (3.90%)
occurrences (all)	0	3	3
Hypoaesthesia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Lymphadenitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Middle ear inflammation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Eye disorders			
Blindness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis allergic			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Enteritis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Salivary gland pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Food poisoning			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Eczema			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Dermatitis atopic			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Nail bed inflammation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Pruritus allergic			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Thyroid cyst			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Myositis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Bacteraemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Dental fistula			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Dermatophytosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	1 / 23 (4.35%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Gastroenteritis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Herpangina			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	0 / 77 (0.00%)
occurrences (all)	0	3	0
Otitis externa			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Otitis media acute			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Pharyngotonsillitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Viral pharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Appendicitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Tracheobronchitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	1 / 23 (4.35%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Varicella			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Dyslipidaemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Obesity			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Insulin resistance			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Lipid metabolism disorder			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2018	The amendment included following: - Primary change was related to the sample size justification. Upon review of the pooled blinded data of the primary endpoint, the SD for the primary endpoint (change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the WD Phase in seDBP between AZM and placebo) was 7.82 mmHg which was much less than what had been previously specified. Given variability in the SD, an SD estimate of 8.3 mmHg was to be used in the revised sample size justification. Assuming an SD for the primary endpoint (change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the WD Phase in seDBP between AZM and placebo) of 8.3 mmHg and an overall 10% dropout rate, 156 participants (78 pooled AZM versus 78 pooled Placebo) would provide >80% power to detect a difference of 4.5 mmHg between the pooled AZM group and placebo by a 2-sample t-test of the mean seDBP change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the WD Phase at the 0.05 significance level (2-sided). Prior to the final protocol amendment, the approximate expected percentage of participant with secondary hypertension was to be between 40% to 60% and no more than approximately 25% of participants were to be post-renal transplant participants and no more than approximately 60% of participants were to weigh greater than or equal to 50 kg at Baseline.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported