



Clinical trial results:

A multicenter, 52 to 104 week extension study to evaluate the long term growth and development of pediatric hypertensive patients 6–17 years of age treated previously with aliskiren

Summary

EudraCT number	2011-004411-22
Trial protocol	Outside EU/EEA SK PL
Global end of trial date	02 August 2017

Results information

Result version number	v1 (current)
This version publication date	19 August 2020
First version publication date	19 August 2020

Trial information

Trial identification

Sponsor protocol code	CSPP100A2365E2
-----------------------	----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01420068
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 August 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long term growth and development of pediatric hypertensive patients aged 6 – 17 years when treated previously with aliskiren

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2011
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	Poland: 5
Country: Number of subjects enrolled	Slovakia: 24
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United States: 49
Country: Number of subjects enrolled	Guatemala: 7
Country: Number of subjects enrolled	Hungary: 20
Worldwide total number of subjects	106
EEA total number of subjects	49

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)	58

Adolescents (12-17 years)	48
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of a Screening phase, a 4-week dose response phase (Phase 1), followed by a 4-week placebo controlled withdrawal phase (Phase 2).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Enalapril

Arm description:

No study treatment (aliskiren or enalapril) was administered in this off-therapy non-interventional second extension study. The arm/group in this second extension study refers to the actual treatment arm/group assigned at the end of the first extension study (Study CSPP100A2365E1: ClinicalTrials.gov Identifier: NCT01151410). During Study CSPP100A2365E1, participants were to receive one of the following doses of enalapril based on their weight: low weight (≥ 20 to < 50 kg) participants - starting dose 2.5 mg with optional titration to 5 and then 10 mg; mid weight (≥ 50 to < 80 kg) participants - starting dose 5 mg with optional titration to 10 and then 20 mg; high weight (≥ 80 to ≤ 150 kg) participants - starting dose 10 mg with optional titration to 20 and then 40 mg.

Arm type	Off-therapy Extension Study
Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received one of the following doses based on their weight: Low weight (≥ 20 to < 50 kg) patients: Starting dose 2.5 mg with optional titration to 5 and then 10 mg Mid weight (≥ 50 to < 80 kg) patients: Starting dose 5 mg with optional titration to 10 and then 20 mg High weight (≥ 80 to ≤ 150 kg) patients: Starting dose 10 mg with optional titration to 20 and then 40 mg

Arm title	Aliskiren
------------------	-----------

Arm description:

No study treatment (aliskiren or enalapril) was administered in this off-therapy non-interventional second extension study. The arm/group in this second extension study refers to the actual treatment arm/group assigned at the end of the first extension study (Study CSPP100A2365E1: ClinicalTrials.gov Identifier: NCT01151410). During Study CSPP100A2365E1, participants were to receive one of the following doses of aliskiren based on their weight: low weight (≥ 20 to < 50 kg) participants - starting dose 37.5 mg with optional titration to 75 and then 150 mg; mid weight (≥ 50 to < 80 kg) participants - starting dose 75 mg with optional titration to 150 and then 300 mg; high weight (≥ 80 to ≤ 150 kg) participants - starting dose 150 mg with optional titration to 300 and then 600 mg.

Arm type	Off-therapy Extension Study
----------	-----------------------------

Investigational medicinal product name	Aliskiren
Investigational medicinal product code	
Other name	SPP100
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Aliskiren dispensing capsules containing minitables (3.125 mg per minitab) in a low, mid and high dose was dispensed in the previous studies [CSPP100A2365 and/or CSPP100A2365E1].

Number of subjects in period 1	Enalapril	Aliskiren
Started	51	55
Completed	49	50
Not completed	2	5
Consent withdrawn by subject	1	2
Administrative problems	1	3

Baseline characteristics

Reporting groups

Reporting group title	Enalapril
-----------------------	-----------

Reporting group description:

No study treatment (aliskiren or enalapril) was administered in this off-therapy non-interventional second extension study. The arm/group in this second extension study refers to the actual treatment arm/group assigned at the end of the first extension study (Study CSPP100A2365E1: ClinicalTrials.gov Identifier: NCT01151410). During Study CSPP100A2365E1, participants were to receive one of the following doses of enalapril based on their weight: low weight (≥ 20 to < 50 kg) participants - starting dose 2.5 mg with optional titration to 5 and then 10 mg; mid weight (≥ 50 to < 80 kg) participants - starting dose 5 mg with optional titration to 10 and then 20 mg; high weight (≥ 80 to ≤ 150 kg) participants - starting dose 10 mg with optional titration to 20 and then 40 mg.

Reporting group title	Aliskiren
-----------------------	-----------

Reporting group description:

No study treatment (aliskiren or enalapril) was administered in this off-therapy non-interventional second extension study. The arm/group in this second extension study refers to the actual treatment arm/group assigned at the end of the first extension study (Study CSPP100A2365E1: ClinicalTrials.gov Identifier: NCT01151410). During Study CSPP100A2365E1, participants were to receive one of the following doses of aliskiren based on their weight: low weight (≥ 20 to < 50 kg) participants - starting dose 37.5 mg with optional titration to 75 and then 150 mg; mid weight (≥ 50 to < 80 kg) participants - starting dose 75 mg with optional titration to 150 and then 300 mg; high weight (≥ 80 to ≤ 150 kg) participants - starting dose 150 mg with optional titration to 300 and then 600 mg.

Reporting group values	Enalapril	Aliskiren	Total
Number of subjects	51	55	106
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	28	30	58
Adolescents (12-17 years)	23	25	48
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	11.5	11.4	
standard deviation	± 3.32	± 3.21	-
Gender categorical			
Units: Subjects			
Female	19	23	42
Male	32	32	64

End points

End points reporting groups

Reporting group title	Enalapril
-----------------------	-----------

Reporting group description:

No study treatment (aliskiren or enalapril) was administered in this off-therapy non-interventional second extension study. The arm/group in this second extension study refers to the actual treatment arm/group assigned at the end of the first extension study (Study CSPP100A2365E1: ClinicalTrials.gov Identifier: NCT01151410). During Study CSPP100A2365E1, participants were to receive one of the following doses of enalapril based on their weight: low weight (≥ 20 to < 50 kg) participants - starting dose 2.5 mg with optional titration to 5 and then 10 mg; mid weight (≥ 50 to < 80 kg) participants - starting dose 5 mg with optional titration to 10 and then 20 mg; high weight (≥ 80 to ≤ 150 kg) participants - starting dose 10 mg with optional titration to 20 and then 40 mg.

Reporting group title	Aliskiren
-----------------------	-----------

Reporting group description:

No study treatment (aliskiren or enalapril) was administered in this off-therapy non-interventional second extension study. The arm/group in this second extension study refers to the actual treatment arm/group assigned at the end of the first extension study (Study CSPP100A2365E1: ClinicalTrials.gov Identifier: NCT01151410). During Study CSPP100A2365E1, participants were to receive one of the following doses of aliskiren based on their weight: low weight (≥ 20 to < 50 kg) participants - starting dose 37.5 mg with optional titration to 75 and then 150 mg; mid weight (≥ 50 to < 80 kg) participants - starting dose 75 mg with optional titration to 150 and then 300 mg; high weight (≥ 80 to ≤ 150 kg) participants - starting dose 150 mg with optional titration to 300 and then 600 mg.

Primary: Change in Weight Assessments From Baseline (Visit 2 of the Core Study) to Long Term (LT) Visit 18 (Week 104) for the Enrolled to Follow-up Set (EFS)

End point title	Change in Weight Assessments From Baseline (Visit 2 of the Core Study) to Long Term (LT) Visit 18 (Week 104) for the Enrolled to Follow-up Set (EFS)
-----------------	--

End point description:

Participant weight was measured at Baseline (Visit 2 of the Core study), LT Visit 17, LT Visit 18 ([Week 104] only for participants identified in the core study as having primary hypertension), and LT Visit 19 ([Week 156] only for participants identified in the core study as having secondary hypertension). Body weight was measured to the nearest 0.1 kg in indoor clothing, but without shoes.

End point type	Primary
----------------	---------

End point timeframe:

Baseline to LT Visit 18 (Week 104): 2 years (104 weeks)

End point values	Enalapril	Aliskiren		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49 ^[1]	50 ^[2]		
Units: kilogram(s)				
least squares mean (standard error)	8.90 (\pm 1.359)	9.22 (\pm 1.399)		

Notes:

[1] - Consisted of all participants who signed the informed consent form for the second extension study.

[2] - Consisted of all participants who signed the informed consent form for the second extension study.

Statistical analyses

Statistical analysis title	Change in Weight Assessments
Comparison groups	Enalapril v Aliskiren
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.84 ^[4]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.74
upper limit	3.37

Notes:

[3] - Treatment regimen, region, age strata, and hypertension etiology (primary, secondary) as factors, and Baseline weight as covariates.

[4] - p-value for statistical significance at 0.05 level for 2-sided superiority testing.

Primary: Change in Height Assessments From Baseline (Visit 2 of the Core Study) to Long Term (LT) Visit 18 (Week 104) for the EFS

End point title	Change in Height Assessments From Baseline (Visit 2 of the Core Study) to Long Term (LT) Visit 18 (Week 104) for the EFS
-----------------	--

End point description:

Participant height was measured at Baseline (Visit 2 of the Core study), LT Visit 17, LT Visit 18 ([Week 104] only for participants identified in the core study as having primary hypertension), and LT Visit 19 ([Week 156] only for participants identified in the core study as having secondary hypertension).

End point type	Primary
----------------	---------

End point timeframe:

Change in Height Assessments From Baseline (Visit 2 of the Core Study) to Long Term (LT) Visit 18 (Week 104) for the EFS

End point values	Enalapril	Aliskiren		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49 ^[5]	50 ^[6]		
Units: centimetre				
least squares mean (standard error)	7.27 (± 0.586)	7.96 (± 0.607)		

Notes:

[5] - Consisted of all participants who signed the informed consent form for the second extension study.

[6] - Consisted of all participants who signed the informed consent form for the second extension study.

Statistical analyses

Statistical analysis title	Change in Height Assessments
-----------------------------------	------------------------------

Statistical analysis description:

Treatment regimen, region, age strata, and hypertension etiology (primary, secondary) as factors, and Baseline height as covariates.

Comparison groups	Enalapril v Aliskiren
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.303 ^[7]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	2.02

Notes:

[7] - p-value for statistical significance at 0.05 level for 2-sided superiority testing.

Primary: Change in BMI Assessments From Baseline (Visit 2 of the Core Study) to Long Term (LT) Visit 18 (Week 104) for the EFS

End point title	Change in BMI Assessments From Baseline (Visit 2 of the Core Study) to Long Term (LT) Visit 18 (Week 104) for the EFS
-----------------	---

End point description:

Participant height and weight was measured at Baseline (Visit 2 of the Core study), LT Visit 17, LT Visit 18 ([Week 104] only for participants identified in the core study as having primary hypertension), and LT Visit 19 ([Week 156] only for participants identified in the core study as having secondary hypertension). BMI was derived.

End point type	Primary
----------------	---------

End point timeframe:

Baseline to LT Visit 18 (Week 104): 2 years (104 weeks)

End point values	Enalapril	Aliskiren		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49 ^[8]	50 ^[9]		
Units: kg/m ²				
least squares mean (standard error)	1.53 (± 0.487)	1.56 (± 0.502)		

Notes:

[8] - Consisted of all participants who signed the informed consent form for the second extension study.

[9] - Consisted of all participants who signed the informed consent form for the second extension study.

Statistical analyses

Statistical analysis title	Change in BMI Assessments
----------------------------	---------------------------

Statistical analysis description:

Treatment regimen, region, age strata, and hypertension etiology (primary, secondary) as factors, and Baseline BMI as covariates.

Comparison groups	Enalapril v Aliskiren
-------------------	-----------------------

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.957 ^[10]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	1.12

Notes:

[10] - p-value for statistical significance at 0.05 level for 2-sided superiority testing.

Primary: Change in Neurocognitive Assessments From Baseline (Visit 2 of the Core Study) to Long Term (LT) Visit 18 (Week 104) for the EFS

End point title	Change in Neurocognitive Assessments From Baseline (Visit 2 of the Core Study) to Long Term (LT) Visit 18 (Week 104) for the EFS ^[11]
-----------------	--

End point description:

All participants who were determined to have secondary hypertension in the core study and had a Baseline (Visit 2) standardized neurocognitive assessment in the core study received follow-up neurocognitive assessments at LT Visit 18 and LT Visit 19 with the same tool. The neurocognitive assessment of development included assessment of the following abilities: Attention, Processing speed, Working memory, and Motor speed. For Numbers (Forward and Backward Raw Score), Visual Matching (Number Correct), Sequences (Total Raw Score): positive change indicates a numerical increase, which is considered a better outcome/improvement; negative change/numerical decrease is considered a worse outcome/decline. For Visual Matching (Time to Complete), Time Tapping (Right and Left Hands), and Timed Gait: positive change indicates a numerical increase, which is considered a worse outcome/decline; negative change/numerical decrease is considered a better outcome/improvement.

End point type	Primary
----------------	---------

End point timeframe:

Baseline to LT Visit 18 (Week 104): 2 years (104 weeks)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were reported for this primary end point.

End point values	Enalapril	Aliskiren		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8 ^[12]	6 ^[13]		
Units: Count of Participants				
number (not applicable)				
Numbers: Forward raw score - Positive change	8	4		
Numbers: Forward raw score - No change	0	1		
Numbers: Forward raw score - Negative change	0	1		
Numbers: Backward raw score - Positive change	5	4		
Numbers: Backward raw score - No change	2	1		

Numbers: Backward raw score - Negative change	1	1		
Visual matching: Number correct - Positive change	7	6		
Visual matching: Number correct - No change	0	0		
Visual matching: Number correct - Negative change	1	0		
Visual matching: Time to complete-sec - Pos change	0	0		
Visual matching: Time to complete-sec - No change	7	6		
Visual matching: Time to complete-sec - Neg change	1	0		
Sequences: Total raw score - Positive change	6	6		
Sequences: Total raw score - No change	1	0		
Sequences: Total raw score - Negative change	1	0		
Time tapping: Right hand - Positive change	7	3		
Time tapping: Right hand - No change	0	0		
Time tapping: Right hand - Negative change	1	3		
Time tapping: Left hand - Positive change	4	2		
Time tapping: Left hand - No change	3	2		
Time tapping: Left hand - Negative change	1	2		
Timed gait: Number of seconds- Positive change	4	3		
Timed gait: Number of seconds- No change	3	0		
Timed gait: Number of seconds- Negative change	1	2		

Notes:

[12] - Consisted of all participants who signed the informed consent form for the second extension study.

[13] - Consisted of all participants who signed the informed consent form. Timed gait: Number of seconds =5

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Weight Assessments From Baseline (Visit 2 of the Core Study) to End of Study (EOS) by Hypertension Group

End point title	Change in Weight Assessments From Baseline (Visit 2 of the Core Study) to End of Study (EOS) by Hypertension Group
-----------------	--

End point description:

Participant weight was measured at Baseline (Visit 2 of the Core study), LT Visit 17, LT Visit 18 ([Week 104] only for participants identified in the core study as having primary hypertension), and LT Visit 19 ([Week 156] only for participants identified in the core study as having secondary hypertension). Body weight was measured to the nearest 0.1 kg in indoor clothing, but without shoes.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline to EOS (2 to 3 years). EOS was defined as LT Visit 18 (Week 104) and LT Visit 19 (Week 156) for participants with primary and secondary hypertension, respectively.

End point values	Enalapril	Aliskiren		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41 ^[14]	44 ^[15]		
Units: kilogram(s)				
least squares mean (standard error)				
Primary Hypertension Group	8.31 (± 1.195)	8.33 (± 1.182)		
Secondary Hypertension Group	-0.73 (± 3.699)	-3.80 (± 3.445)		

Notes:

[14] - Consisted of all participants who signed the ICF for the second extension study. N= 41, 8

[15] - Consisted of all participants who signed the ICF for the second extension study. N= 44, 7

Statistical analyses

Statistical analysis title	Change in Weight Assessments - Primary
----------------------------	--

Statistical analysis description:

Primary Hypertension group (at LT Visit 18 [Week 104])

Treatment regimen, region, age strata, and Baseline weight as covariates

Comparison groups	Enalapril v Aliskiren
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.992 ^[16]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.29
upper limit	3.33

Notes:

[16] - p-value for statistical significance at 0.05 level for 2-sided superiority testing.

Statistical analysis title	Change in Weight Assessments - Secondary
----------------------------	--

Statistical analysis description:

Secondary hypertension group (at LT Visit 19 [Week 156])

Treatment regimen, region, age strata, and Baseline weight as covariates.

Comparison groups	Enalapril v Aliskiren
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.215 ^[17]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.22
upper limit	2.1

Notes:

[17] - p-value for statistical significance at 0.05 level for 2-sided superiority testing.

Secondary: Change in Height Assessments From Baseline (Visit 2 of the Core Study) to EOS by Hypertension Group

End point title	Change in Height Assessments From Baseline (Visit 2 of the Core Study) to EOS by Hypertension Group
-----------------	---

End point description:

Participant height was measured at Baseline (Visit 2 of the Core study), LT Visit 17, LT Visit 18 ([Week 104] only for participants identified in the core study as having primary hypertension), and LT Visit 19 ([Week 156] only for participants identified in the core study as having secondary hypertension).

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline to EOS (2 to 3 years). EOS was defined as LT Visit 18 (Week 104) and LT Visit 19 (Week 156) for participants with primary and secondary hypertension, respectively.

End point values	Enalapril	Aliskiren		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41 ^[18]	44 ^[19]		
Units: centimetre				
least squares mean (standard error)				
Primary Hypertension Group	6.80 (± 0.529)	7.42 (± 0.528)		
Secondary Hypertension Group	16.05 (± 3.316)	16.96 (± 3.044)		

Notes:

[18] - Consisted of all participants who signed the ICF for the second extension study. N= 41, 8

[19] - Consisted of all participants who signed the ICF for the second extension study. N= 44, 7

Statistical analyses

Statistical analysis title	Change in Height Assessments - Primary
----------------------------	--

Statistical analysis description:

Primary Hypertension group (at LT Visit 18 [Week 104])

Treatment regimen, region, age strata, and Baseline height as covariates

Comparison groups	Enalapril v Aliskiren
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.403 ^[20]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	2.09

Notes:

[20] - p-value for statistical significance at 0.05 level for 2-sided superiority testing.

Statistical analysis title	Change in Height Assessments - Secondary
-----------------------------------	--

Statistical analysis description:

Secondary hypertension group (at LT Visit 19 [Week 156])

Comparison groups	Enalapril v Aliskiren
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67 ^[21]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.92

Confidence interval

level	95 %
sides	2-sided
lower limit	-3.74
upper limit	5.57

Notes:

[21] - p-value for statistical significance at 0.05 level for 2-sided superiority testing.

Secondary: Change in BMI Assessments From Baseline (Visit 2 of the Core Study) to EOS by Hypertension Group

End point title	Change in BMI Assessments From Baseline (Visit 2 of the Core Study) to EOS by Hypertension Group
-----------------	--

End point description:

Participant weight and height was measured at Baseline (Visit 2 of the Core study), LT Visit 17, LT Visit 18 ([Week 104] only for participants identified in the core study as having primary hypertension), and LT Visit 19 ([Week 156] only for participants identified in the core study as having secondary hypertension). Body weight was measured to the nearest 0.1 kg in indoor clothing, but without shoes. BMI was derived.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline to EOS (2 to 3 years). EOS was defined as LT Visit 18 (Week 104) and LT Visit 19 (Week 156) for participants with primary and secondary hypertension, respectively.

End point values	Enalapril	Aliskiren		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41 ^[22]	44 ^[23]		
Units: kg/m ²				
least squares mean (standard error)				
Primary Hypertension Group	1.30 (± 0.428)	1.19 (± 0.424)		
Secondary Hypertension Group	-1.81 (± 1.336)	-2.97 (± 1.397)		

Notes:

[22] - Consisted of all participants who signed the ICF for the second extension study. N= 41, 8

[23] - Consisted of all participants who signed the ICF for the second extension study. N= 44, 7

Statistical analyses

Statistical analysis title	Change in BMI Assessments - Primary
----------------------------	-------------------------------------

Statistical analysis description:

Primary Hypertension group (at LT Visit 18 [Week 104])

Treatment regimen, region, age strata, and Baseline BMI as covariates

Comparison groups	Enalapril v Aliskiren
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86 ^[24]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	1.08

Notes:

[24] - p-value for statistical significance at 0.05 level for 2-sided superiority testing.

Statistical analysis title	Change in BMI Assessments - Secondary
----------------------------	---------------------------------------

Statistical analysis description:

Secondary hypertension group (at LT Visit 19 [Week 156])

Treatment regimen, region, age strata, and Baseline BMI as covariates.

Comparison groups	Enalapril v Aliskiren
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32 ^[25]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.66
upper limit	1.32

Notes:

[25] - p-value for statistical significance at 0.05 level for 2-sided superiority testing.

Secondary: Change in Neurocognitive Assessments From Baseline (Visit 2 of the Core Study) to EOS by Hypertension Group

End point title	Change in Neurocognitive Assessments From Baseline (Visit 2 of the Core Study) to EOS by Hypertension Group
-----------------	---

End point description:

All participants who were determined to have secondary hypertension in the core study and had a Baseline (Visit 2) standardized neurocognitive assessment in the core study received follow-up neurocognitive assessments at LT Visit 18 and LT Visit 19 with the same tool. The neurocognitive assessment of development included assessment of the following abilities: Attention, Processing speed, Working memory, and Motor speed. For Numbers (Forward and Backward Raw Score), Visual Matching (Number Correct), Sequences (Total Raw Score): positive change indicates a numerical increase, which is considered a better outcome/improvement; negative change/numerical decrease is considered a worse outcome/decline. For Visual Matching (Time to Complete), Time Tapping (Right and Left Hands), and Timed Gait: positive change indicates a numerical increase, which is considered a worse outcome/decline; negative change/numerical decrease is considered a better outcome/improvement.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline to EOS (3 years). EOS was defined as LT Visit 19 (Week 156) for participants with secondary hypertension.

End point values	Enalapril	Aliskiren		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8 ^[26]	6 ^[27]		
Units: participants				
number (not applicable)				
Numbers: Forward raw score: Positive change	7	5		
Numbers: Forward raw score: No change	1	0		
Numbers: Forward raw score: Negative change	0	1		
Numbers: Backward raw score: Positive change	5	4		
Numbers: Backward raw score: No change	2	1		
Numbers: Backward raw score: Negative change	1	1		
Visual matching: Number correct: Positive change	6	6		
Visual matching: Number correct: No change	0	0		
Visual matching: Number correct: Negative change	2	0		
Visual matching: Time to complete: Positive change	0	0		
Visual matching: Time to complete: No change	7	6		
Visual matching: Time to complete: Negative change	1	0		
Sequences: Total raw score: Positive change	8	6		

Sequences: Total raw score: No change	0	0		
Sequences: Total raw score: Negative change	0	0		
Time tapping: Right hand: Positive change	5	1.076		
Time tapping: Right hand: No change	2	1		
Time tapping: Right hand: Negative change	1	4		
Time tapping: Left hand: Positive change	2	2		
Time tapping: Left hand: No change	3	1		
Time tapping: Left hand: Negative change	3	3		
Timed gait: Number of seconds: Positive change	4	3		
Timed gait: Number of seconds: No change	2	0		
Timed gait: Number of seconds: Negative change	2	3		

Notes:

[26] - The EFS consisted of all participants who signed the ICF for the second extension study.

[27] - The EFS consisted of all participants who signed the ICF for the second extension study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

This study only collected the occurrence of Serious Adverse Events (SAEs) occurring within the first 30 days after the participant had completed the first extension study. SAEs experienced after this 30 day period were reported to Novartis/Noden.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Enalapril
-----------------------	-----------

Reporting group description:

No study treatment (aliskiren or enalapril) was administered in this off-therapy non-interventional second extension study. The arm/group in this second extension study refers to the actual treatment arm/group assigned at the end of the first extension study (Study CSPP100A2365E1: ClinicalTrials.gov Identifier: NCT01151410). During Study CSPP100A2365E1, participants were to receive one of the following doses of enalapril based on their weight: low weight (≥ 20 to < 50 kg) participants - starting dose 2.5 mg with optional titration to 5 and then 10 mg; mid weight (≥ 50 to < 80 kg) participants - starting dose 5 mg with optional titration to 10 and then 20 mg; high weight (≥ 80 to ≤ 150 kg) participants - starting dose 10 mg with optional titration to 20 and then 40 mg.

Reporting group title	Aliskiren
-----------------------	-----------

Reporting group description:

No study treatment (aliskiren or enalapril) was administered in this off-therapy non-interventional second extension study. The arm/group in this second extension study refers to the actual treatment arm/group assigned at the end of the first extension study (Study CSPP100A2365E1: ClinicalTrials.gov Identifier: NCT01151410). During Study CSPP100A2365E1, participants were to receive one of the following doses of aliskiren based on their weight: low weight (≥ 20 to < 50 kg) participants - starting dose 37.5 mg with optional titration to 75 and then 150 mg; mid weight (≥ 50 to < 80 kg) participants - starting dose 75 mg with optional titration to 150 and then 300 mg; high weight (≥ 80 to ≤ 150 kg) participants - starting dose 150 mg with optional titration to 300 and then 600 mg.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: There were no non-serious adverse events reported in this study.

Serious adverse events	Enalapril	Aliskiren	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 51 (1.96%)	0 / 55 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Phimosi			
subjects affected / exposed	1 / 51 (1.96%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Enalapril	Aliskiren	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 51 (0.00%)	0 / 55 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to small sample sizes in the secondary hypertension etiology subgroups, the corresponding p-values for treatment comparisons should be interpreted with caution.
--

Notes: