



Clinical trial results:

A Randomized Double-blind, Placebo-controlled, Multi-center, Cross-over Study of Rosuvastatin in Children and Adolescents (aged 6 to <18 years) with Homozygous Familial Hypercholesterolemia (HoFH)

Summary

EudraCT number	2014-000972-24
Trial protocol	SE NL BE DK DE
Global end of trial date	02 July 2015

Results information

Result version number	v1 (current)
This version publication date	07 April 2016
First version publication date	07 April 2016

Trial information

Trial identification

Sponsor protocol code	D3561C00004
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Astra Zeneca R&D
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, 43183
Public contact	Stefan C. Carlsson, Astra Zeneca R&D, Stefan.Carlsson@astrazeneca.com
Scientific contact	Stefan C. Carlsson, Astra Zeneca R&D Mölndal R&D, Stefan.Carlsson@astrazeneca.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2015
Global end of trial reached?	Yes
Global end of trial date	02 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the efficacy of rosuvastatin 20 mg on LDL-C, compared to placebo, after 6 weeks of treatment in pediatric HoFH patients

Protection of trial subjects:

None

Background therapy:

Ezetimibe and apheresis treatments were allowed during the study if initiated before study enrolment

Evidence for comparator: -

Actual start date of recruitment	03 November 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 2
Worldwide total number of subjects	20
EEA total number of subjects	8

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)	7
Adolescents (12-17 years)	13
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

20 patients recruited at centers within 8 countries (Belgium, Canada, Denmark, Israel, Malaysia, Sweden, Taiwan, and The Netherlands) that participated in the study. FSI date: 03-Nov-2014.

Pre-assignment

Screening details:

20 enrolled, 3 withdrew consent, 3 did not fulfil eligibility criteria. Among the 14 left, 10 went through 4 week lead-in phase and 4 did not.

Period 1

Period 1 title	Screening
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Screening
Arm description: -	
Arm type	Screening
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Screening
Started	20
Completed	14
Not completed	6
3 consent 3 criteria	6

Period 2

Period 2 title	Lead-in
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Lead-in
Arm description: -	
Arm type	Lead-in
Investigational medicinal product name	Rosuvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Tablet
Routes of administration	Oral use, Oral use

Dosage and administration details:

10mg QED

Number of subjects in period 2	Lead-in
Started	14
Completed	14

Period 3

Period 3 title	Cross-over
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Data analyst, Investigator, Monitor, Carer, Assessor

Arms

Arm title	Cross-over
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Rosuvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20mg QED

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is not the baseline period. Rather baseline is defined as the last measurement before the first dose of randomized study drug in the cross-over phase.

Number of subjects in period 3^[2]	Cross-over
Started	14
Completed	13
Not completed	1
Consent withdrawn by subject	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification:

The number of subjects reported in the baseline period is not the same as the worldwide number enrolled in the trial as 6 of the 20 subjects did not have baseline measurements.

Period 4

Period 4 title	Maintenance
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Maintenance
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Rosuvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20mg QED

Number of subjects in period 4	Maintenance
Started	13
Completed	13

Baseline characteristics

Reporting groups

Reporting group title	Cross-over
Reporting group description:	
Safety Analysis Set	

Reporting group values	Cross-over	Total	
Number of subjects	14	14	
Age Categorical			
Age Groups are Children (6-9 years) and Adolescents (10-17 years)			
Units: Subjects			
Children (6-9 years)	4	4	
Adolescents (10-17 years)	10	10	
Age Continuous			
Units: years			
arithmetic mean	10.9		
standard deviation	± 2.7	-	
Gender Categorical			
Units: Subjects			
Female	7	7	
Male	7	7	

Subject analysis sets

Subject analysis set title	C-FAS PLACEBO
Subject analysis set type	Full analysis
Subject analysis set description:	
Cross-over Full Analysis Set, 6 weeks of Placebo	
Subject analysis set title	C-FAS ROSUVASTATIN
Subject analysis set type	Full analysis
Subject analysis set description:	
Cross-over Full Analysis Set, 6 weeks of rosuvastatin	

Reporting group values	C-FAS PLACEBO	C-FAS ROSUVASTATIN	
Number of subjects	13	13	
Age Categorical			
Age Groups are Children (6-9 years) and Adolescents (10-17 years)			
Units: Subjects			
Children (6-9 years)	4	4	
Adolescents (10-17 years)	9	9	
Age Continuous			
Units: years			
arithmetic mean	10.9	10.9	
standard deviation	± 2.7	± 2.7	
Gender Categorical			
Units: Subjects			
Female	6	6	

Male	7	7	
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End points

End points reporting groups

Reporting group title	Screening
Reporting group description: -	
Reporting group title	Lead-in
Reporting group description: -	
Reporting group title	Cross-over
Reporting group description: -	
Reporting group title	Maintenance
Reporting group description: -	
Subject analysis set title	C-FAS PLACEBO
Subject analysis set type	Full analysis
Subject analysis set description: Cross-over Full Analysis Set, 6 weeks of Placebo	
Subject analysis set title	C-FAS ROSUVASTATIN
Subject analysis set type	Full analysis
Subject analysis set description: Cross-over Full Analysis Set, 6 weeks of rosuvastatin	

Primary: LDL-C during Cross-over phase

End point title	LDL-C during Cross-over phase
End point description: 7 patients had 6 weeks of rosuvastatin followed by 6 weeks of placebo and 6 patients had 6 weeks of placebo followed by 6 weeks of rosuvastatin	
End point type	Primary
End point timeframe: LDL-C	

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATIN		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: mg/dL				
number (standard deviation)				
mg/dL	481.4	396		
mmol/L	12.47	10.26		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description: The response was log LDL-C at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors were treatment and period. Subject/patient was a random factor	
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Relative diff in geometric LS means
Point estimate	-22.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.5
upper limit	-9.1

Secondary: LDL-C during Cross-over phase, non-apheresis

End point title	LDL-C during Cross-over phase, non-apheresis
End point description:	Efficacy in terms of low density lipoprotein cholesterol (LDL C) following 6 weeks rosuvastatin 20 mg or placebo treatment in patients not treated with Apheresis
End point type	Secondary
End point timeframe:	
Samples taken at Day 42 (week 6) and Day 84 (week 12)	

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATI N		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: mg/dL				
arithmetic mean (standard deviation)				
mg/dL	594.7 (± 203.6)	479.8 (± 239.07)		
mmol/L	15.4 (± 5.274)	12.43 (± 6.191)		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description:	The response was log LDL-C at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors where treatment and period. Subject/patient was a random factor
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Mixed models analysis
Parameter estimate	Relative diff in geometric LS means
Point estimate	-26.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.7
upper limit	6

Secondary: HDL-C

End point title	HDL-C
End point description:	
Efficacy in terms of high density lipoprotein cholesterol (HDL C)	
End point type	Secondary
End point timeframe:	
Samples taken at Day 42 (week 6) and Day 84 (week 12)	

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATI N		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: mg/dL				
arithmetic mean (standard deviation)				
mg/dL	33.7 (± 8.47)	35.5 (± 7.29)		
mmol/L	0.87 (± 0.218)	0.92 (± 0.189)		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description:	
The response was log HDL-C at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors were treatment and period. Subject/patient was a random factor	
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.314
Method	Mixed models analysis
Parameter estimate	Relative diff in geometric LS means
Point estimate	7.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	24.5

Secondary: Triglycerides during Cross-over phase

End point title	Triglycerides during Cross-over phase
End point description:	
Efficacy in terms of triglycerides (TG)	
End point type	Secondary
End point timeframe:	
Samples taken at Day 42 (week 6) and Day 84 (week 12)	

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATI N		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: mg/dL				
arithmetic mean (standard deviation)				
mg/dL	119.5 (± 52.67)	79.8 (± 24.48)		
mmol/L	1.35 (± 0.595)	0.9 (± 0.277)		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description:	
The response was log triglycerides at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors were treatment and period. Subject/patient was a random factor	
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Relative diff in geometric LS means
Point estimate	-30.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.2
upper limit	-13.3

Secondary: LDL-C/HDL-C during Cross-over phase

End point title	LDL-C/HDL-C during Cross-over phase
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End point description:

Efficacy in terms of low density lipoprotein cholesterol (LDL C) / high density lipoprotein cholesterol (HDL C)

End point type	Secondary
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End point timeframe:

Samples taken at Day 42 (week 6) and Day 84 (week 12)

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATI N		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: N/A				
arithmetic mean (standard deviation)	15.6 (± 9.1317)	12.208 (± 7.8638)		

Statistical analyses

Statistical analysis title	Mixed model analysis
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Statistical analysis description:

The response was log LDL-C/HDL-C at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors

where treatment and period. Subject/patient was a random factor

Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN
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Number of subjects included in analysis	26
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.006
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Method	Mixed models analysis
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Parameter estimate	Relative diff in geometric LS means
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Point estimate	-27.6
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-41.2
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upper limit	-11
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Secondary: TC/HDL-C during Cross-over phase

End point title	TC/HDL-C during Cross-over phase
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End point description:	
Efficacy in terms of total cholesterol (TC) / high density lipoprotein cholesterol (HDL C)	
End point type	Secondary
End point timeframe:	
Samples taken at Day 42 (week 6) and Day 84 (week 12)	

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATIN		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: N/A				
arithmetic mean (standard deviation)	17.416 ($\pm$ 9.5454)	13.704 ($\pm$ 8.0414)		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description:	
The response was log TC/HDL-C at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors where treatment and period. Subject/patient was a random factor	
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Relative diff in geometric LS means
Point estimate	-25.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.1
upper limit	-10.5

Secondary: Non-HDL-C/HDL-C during Cross-over phase

End point title	Non-HDL-C/HDL-C during Cross-over phase
End point description:	
Efficacy in terms of non-high density lipoprotein cholesterol (non-HDL C) / HDL C	
End point type	Secondary
End point timeframe:	
Samples taken at Day 42 (week 6) and Day 84 (week 12)	

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATIN		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: N/A				
arithmetic mean (standard deviation)	16.416 ($\pm$ 9.5454)	12.704 ($\pm$ 8.0414)		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description:	
The response was log Non-HDL-C/HDL-C at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors were treatment and period. Subject/patient was a random factor	
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Relative diff in geometric LS means
Point estimate	-28.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.7
upper limit	-11.4

Secondary: Apo A-1 during Cross-over phase

End point title	Apo A-1 during Cross-over phase
End point description:	
Efficacy in terms of apolipoprotein A-1 (Apo A-1)	
End point type	Secondary
End point timeframe:	
Samples taken at Day 42 (week 6) and Day 84 (week 12)	

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATI N		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: mg/dL				
arithmetic mean (standard deviation)				
mg/dL	100 ($\pm$ 17.65)	103.5 ($\pm$ 17.28)		
g/L	1 ($\pm$ 0.177)	1.03 ($\pm$ 0.173)		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description:	
The response was log Apo A-1 at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors where treatment and period. Subject/patient was a random factor	
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.383
Method	Mixed models analysis
Parameter estimate	Relative diff in geometric LS means
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	14.6

Secondary: Apo B/Apo A-1 during Cross-over phase

End point title	Apo B/Apo A-1 during Cross-over phase
End point description:	
Efficacy in terms of apolipoprotein B (Apo B) / apolipoprotein A-1 (Apo A-1)	
End point type	Secondary
End point timeframe:	
Samples taken at Day 42 (week 6) and Day 84 (week 12)	

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATI N		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: N/A				
arithmetic mean (standard deviation)	2.873 ($\pm$ 1.4669)	2.408 ($\pm$ 1.3259)		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description:	
The response was log Apo B/Apo A-1 at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors where treatment and period. Subject/patient was a random factor	
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Mixed models analysis
Parameter estimate	Relative diff in geometric LS means
Point estimate	-20.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.8
upper limit	-5.6

Secondary: LDL-C from End of Placebo Period to End of Study

End point title	LDL-C from End of Placebo Period to End of Study
End point description:	
Change in low density lipoprotein cholesterol (LDL C) from end of placebo period to 6, 12, and 18 weeks of therapy with rosuvastatin 20 mg	
End point type	Secondary
End point timeframe:	
Samples taken at Day 42 (week 6), Day 84 (week 12), Day 126 (week 18) and Day 168 (week 24)	

End point values	Cross-over			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: mg/dL				
arithmetic mean (standard deviation)				
LDL-C eop (n=13) mg/dL	481.4 ($\pm$ 184.9)			

LDL-C 6 wks after eop (n=13) mg/dL	409.7 (± 209.97)			
LDL-C 12 wks after eop (n=11) mg/dL	372.5 (± 187.11)			
LDL-C 18 wks after eop (n=5) mg/dL	441.8 (± 260.31)			
LDL-C eop (n=13) mmol/L	12.47 (± 4.79)			
LDL-C 6 wks after eop (n=13) mmol/L	10.61 (± 5.438)			
LDL-C 12 wks after eop (n=11) mmol/L	9.65 (± 4.845)			
LDL-C 18 wks after eop (n=5) mmol/L	11.44 (± 6.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rosuvastatin Trough Concentrations

End point title	Rosuvastatin Trough Concentrations
End point description:	Pharmacokinetic profile in terms of trough concentrations
End point type	Secondary
End point timeframe:	Samples taken at Day 42 (week 6), Day 84 (week 12), Day 126 (week 18)

End point values	Cross-over	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11 ^[1]	13 ^[2]		
Units: ng/mL				
arithmetic mean (standard deviation)				
ng/mL	7.387 (± 8.11)	4.482 (± 3.5)		

Notes:

[1] - Measurement taken after 6 weeks active treatment (rosuvastatin) in cross-over phase

[2] - Measurement taken after 6 weeks active treatment (rosuvastatin) in maintenance phase

Statistical analyses

No statistical analyses for this end point

Secondary: Total Cholesterol during Cross-over phase

End point title	Total Cholesterol during Cross-over phase
End point description:	Efficacy in terms of total cholesterol (TC)
End point type	Secondary
End point timeframe:	Samples taken at Day 42 (week 6) and Day 84 (week 12)

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATIN		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: mg/dL				
arithmetic mean (standard deviation)				
mg/dL	539 (± 184.91)	447.6 (± 195.46)		
mmol/L	13.96 (± 4.79)	11.59 (± 5.063)		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description: The response was log TC at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors where treatment and period. Subject/patient was a random factor	
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Relative diff in geometric LS means
Point estimate	-20.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.7
upper limit	-9.1

Secondary: Non-HDL-C during Cross-over phase

End point title	Non-HDL-C during Cross-over phase
End point description:	
End point type	Secondary
End point timeframe: Samples taken at Day 42 (week 6) and Day 84 (week 12)	

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATI N		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: mg/dL				
arithmetic mean (standard deviation)				
mg/dL	505.3 (± 186.39)	412.1 (± 198.62)		
mmol/L	13.09 (± 4.826)	10.67 (± 5.144)		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description:	
The response was log Non-HDL-C at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors were treatment and period. Subject/patient was a random factor	
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Relative Diff in geometric LS means
Point estimate	-22.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.7
upper limit	-10.3

Secondary: Apo B during Cross-over phase

End point title	Apo B during Cross-over phase
End point description:	
End point type	Secondary
End point timeframe:	
Samples taken at Day 42 (week 6) and Day 84 (week 12)	

End point values	C-FAS PLACEBO	C-FAS ROSUVASTATI N		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: mg/dL				
arithmetic mean (standard deviation)				
mg/dL	267.9 (± 86.33)	234.9 (± 107.02)		
g/L	2.68 (± 0.863)	2.35 (± 1.07)		

Statistical analyses

Statistical analysis title	Mixed model analysis
Statistical analysis description:	
The response was log Apo B at 6 weeks and 12 weeks of the Cross-over phase and the fixed factors were treatment and period. Subject/patient was a random factor	
Comparison groups	C-FAS PLACEBO v C-FAS ROSUVASTATIN
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Mixed models analysis
Parameter estimate	Relative diff in geometric LS means
Point estimate	-17.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.2
upper limit	-2.9

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs will be collected from the time of signature of informed consent throughout the efficacy maintenance phase and including the follow-up of unresolved adverse events; SAEs will be recorded up to 30 days after the last dose of study drug

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Cross-over
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Reporting group description: -	
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Reporting group title	Lead-in
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Reporting group description:	
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Optional Lead-in phase	
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Reporting group title	Maintenance
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Reporting group description:	
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Maintenance phase	
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Reporting group title	Screening
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Reporting group description: -	
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Serious adverse events	Cross-over	Lead-in	Maintenance
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
presyncope	Additional description: Several presyncope episodes		
subjects affected / exposed	0 / 14 (0.00%)	0 / 11 (0.00%)	0 / 13 (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

Serious adverse events	Screening		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
presyncope	Additional description: Several presyncope episodes		

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cross-over	Lead-in	Maintenance
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)	3 / 11 (27.27%)	1 / 13 (7.69%)
Investigations			
Blood bicarbonate decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	2 / 14 (14.29%)	2 / 11 (18.18%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
Peripheral swelling			
subjects affected / exposed	0 / 14 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 14 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Screening		
Total subjects affected by non-serious			

adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
Investigations			
Blood bicarbonate decreased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Peripheral swelling			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2014	1) Patients entering the study on 20 mg or more of rosuvastatin are permitted to receive rosuvastatin 20 mg during the lead-in phase of the study. 2) Patients entering the study on 10 mg or more of rosuvastatin who do not require washout of any dyslipidemia medication, are permitted to forego the lead-in phase and proceed directly to the cross-over phase of the study. 3) PK samples will be drawn at Visits 4, 5, and 6, instead of Visits 6 and 7. 4) Temperature is not required to be taken orally – i.e., it will be permitted to be taken by any route (oral, ear, axillary, rectal).
08 December 2014	1) Statistical updates were made regarding the primary and secondary analyses and the addition of subgroup analyses. 2) "or currently lactating" was added to Exclusion Criterion #21. 3) An assessment of urinary albumin/creatinine ratio was added to the procedures identified in the study plan (Table 1) and to Table 2 for the urinalysis laboratory variables. Additionally, the estimated glomerular filtration rate by Schwartz formula was added to the clinical chemistry assessments listed in Table 2. 4) Text was added regarding the management of repeat/unscheduled laboratories. 5) Text regarding laboratory values outside the reference limits was modified. 6) Appendix E was updated to reflect lab management changes; additional details were added to provide guidance on the actions that should occur if creatine kinase (CK) was found to be >10xULN, and for CK 5-10xULN.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported