



Clinical trial results:

An Open-Label Long-Term Extension to the 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	2014-004746-99
Trial protocol	BE SE DK
Global end of trial date	21 March 2017

Results information

Result version number	v1 (current)
This version publication date	07 May 2017
First version publication date	07 May 2017

Trial information

Trial identification

Sponsor protocol code	D365NC00001
-----------------------	-------------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	AstraZeneca Global Regulatory Affairs, Södertälje, Sweden, S-15185
Public contact	Information Centre, AstraZeneca, information.center@astrazeneca.com
Scientific contact	Information Centre, AstraZeneca, information.center@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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2016
Global end of trial reached?	Yes
Global end of trial date	21 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The safety objective of the study was to assess the long-term safety and tolerability of rosuvastatin 20 mg in pediatric patients with HoFH. The efficacy objective of the study was to assess the longitudinal profile of rosuvastatin 20 mg on lipid parameters (LDL-C, high-density lipoprotein cholesterol [HDL-C], TC, triglycerides [TG], non-HDL-C, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, apolipoprotein A-1 [ApoA-1], and ApoB/ApoA-1). The PK objective of the study was to characterize the trough plasma exposure of rosuvastatin in pediatric patients with HoFH who were up-titrated to a daily dose of rosuvastatin 40 mg.

Protection of trial subjects:

Yada yada

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 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	Belgium: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Taiwan: 2
Worldwide total number of subjects	9
EEA total number of subjects	2

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	0

months)	
Children (2-11 years)	5
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The nine (9) patients recruited were all participants in the D3561C00004 HYDRA study

Pre-assignment

Screening details:

Inclusion criterion was to having completed D3561C00004

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall
-----------	---------

Arm description:

All patients

Arm type	Long term extension
Investigational medicinal product name	Rosuvastatin 20mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

20mg daily

Investigational medicinal product name	Rosuvastatin 40mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

20mg daily

Number of subjects in period 1	Overall
Started	9
Completed	4
Not completed	5
Started on non-allowed con med	3

Baseline characteristics

Reporting groups

Reporting group title	Overall
Reporting group description:	
All patients	

Reporting group values	Overall	Total	
Number of subjects	9	9	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	6	6	
Adolescents (12-17 years)	3	3	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	10.6		
standard deviation	± 2.83	-	
Gender, Male/Female			
Units: Subjects			
Female	4	4	
Male	5	5	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set, comprised of patient who received at least one dose of study drug.	
Subject analysis set title	Sequence A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Rosuva/Placebo in the D3561C00004 cross-over phase	
Subject analysis set title	Sequence B
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Placebo/Rosuva in the D3561C00004 cross-over phase	

Reporting group values	Full analysis set	Sequence A	Sequence B
Number of subjects	9	4	5
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)	6	2	4
Adolescents (12-17 years)	3	2	1
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	10.6	10.8	10.4
standard deviation	± 2.83	± 3.86	± 2.19
Gender, Male/Female Units: Subjects			
Female	4	2	2
Male	5	2	3

End points

End points reporting groups

Reporting group title	Overall
Reporting group description: All patients	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set, comprised of patient who received at least one dose of study drug.	
Subject analysis set title	Sequence A
Subject analysis set type	Intention-to-treat
Subject analysis set description: Rosuva/Placebo in the D3561C00004 cross-over phase	
Subject analysis set title	Sequence B
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo/Rosuva in the D3561C00004 cross-over phase	

Primary: Safety and tolerability in terms of frequency and severity of adverse events, Serious Adverse Events

End point title	Safety and tolerability in terms of frequency and severity of adverse events, Serious Adverse Events ^[1]
End point description:	
End point type	Primary
End point timeframe: 96 weeks	

Notes:

[1] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of frequency and severity of adverse events, Discontinuations due to Adverse Events

End point title	Safety and tolerability in terms of frequency and severity of adverse events, Discontinuations due to Adverse Events ^[2]
End point description:	

End point type	Primary
End point timeframe:	
96 weeks	
Notes:	
[2] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Basophils/Leukocytes (%) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Basophils/Leukocytes (%) >ULN ^[3]
-----------------	--

End point description:

End point type	Primary
End point timeframe:	
96 weeks	

Notes:

[3] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	0		
Week 48	0	0		
Week 60	1	0		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of growth, height

End point title	Safety and tolerability in terms of growth, height ^[4]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[4] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: cm				
arithmetic mean (standard deviation)				
Baseline	142.5 (± 23.57)	136.8 (± 15.02)		
Week 6	143.5 (± 23.57)	136.8 (± 15.32)		
Week 12	144 (± 23.9)	137.6 (± 14.94)		
Week 18	145.3 (± 23.56)	138 (± 14.83)		
Week 24	145.8 (± 24.02)	139.2 (± 15.74)		
Week 36	147 (± 24.15)	140.6 (± 15.61)		
Week 48	148.8 (± 24.25)	142.2 (± 15.21)		
Week 60	158 (± 19.47)	144 (± 16.37)		
Week 72	159 (± 20.22)	145 (± 15.12)		
Week 84	159.7 (± 20.43)	148.3 (± 17.27)		
Week 96	165 (± 25.46)	138 (± 12.73)		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormalitites in sexual maturation

End point title	Safety and tolerability in terms of abnormalitites in sexual maturation ^[5]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[5] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of growth, height SD-score

End point title	Safety and tolerability in terms of growth, height SD-score ^[6]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[6] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: standard deviations				
arithmetic mean (standard deviation)				
Baseline	-0.43 (± 2.025)	-1.05 (± 1.787)		
Week 6	-0.48 (± 1.911)	-1.05 (± 1.871)		
Week 12	-0.41 (± 1.975)	-1.19 (± 1.709)		
Week 18	-0.43 (± 1.61)	-1.14 (± 1.705)		
Week 24	-0.6 (± 1.73)	-0.96 (± 1.67)		

Week 36	-0.43 (± 1.836)	-0.76 (± 1.727)		
Week 48	-0.16 (± 1.781)	-0.72 (± 1.729)		
Week 60	0.05 (± 1.757)	-1.04 (± 1.604)		
Week 72	0 (± 1.635)	-0.87 (± 1.604)		
Week 84	0.08 (± 1.734)	-0.33 (± 1.627)		
Week 96	1.18 (± 0.436)	-0.51 (± 0.886)		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of growth, weight

End point title	Safety and tolerability in terms of growth, weight ^[7]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[7] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: kg				
arithmetic mean (standard deviation)				
Baseline	36.25 (± 14.719)	37.42 (± 16.089)		
Week 6	37.2 (± 16.23)	38.02 (± 16.7)		
Week 12	37.93 (± 17.11)	38.16 (± 17.501)		
Week 18	38.85 (± 17.633)	38.4 (± 16.688)		
Week 24	39.15 (± 17.521)	39 (± 16.704)		
Week 36	39.98 (± 18.293)	39.88 (± 15.015)		
Week 48	41 (± 17.579)	41.16 (± 16.045)		
Week 60	48.47 (± 16.933)	41.8 (± 15.656)		
Week 72	48.43 (± 16.393)	42.1 (± 17.047)		
Week 84	50.17 (± 16.737)	45.28 (± 19.143)		

Week 96	57.35 (\pm 16.476)	33.55 (\pm 2.192)		
---------	-----------------------	----------------------	--	--

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Alanine Aminotransferase (U/L) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Alanine Aminotransferase (U/L) >ULN ^[8]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[8] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	1		
Week 18	0	1		
Week 24	0	0		
Week 36	0	1		
Week 48	0	1		
Week 60	0	1		
Week 72	0	1		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Albumin (g/dL) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Albumin (g/dL) >ULN ^[9]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[9] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	1		
Week 6	0	0		
Week 12	0	0		
Week 18	0	1		
Week 24	0	0		
Week 36	0	0		
Week 48	0	0		
Week 60	0	0		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Aspartate Aminotransferase (U/L) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Aspartate Aminotransferase (U/L) >ULN ^[10]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[10] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	0		
Week 48	0	0		
Week 60	0	1		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Bicarbonate (mol/L) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Bicarbonate (mol/L) <LLN ^[11]
-----------------	--

End point description:

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

End point timeframe:

96 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	1		
Week 12	1	1		
Week 18	0	1		
Week 24	1	1		
Week 36	1	2		
Week 48	1	1		
Week 60	1	3		
Week 72	2	1		
Week 84	1	1		
Week 96	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Bicarbonate (mol/L) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Bicarbonate (mol/L) >ULN ^[12]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[12] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	0		
Week 48	0	0		
Week 60	0	0		
Week 72	0	1		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Ery. Mean Corpuscular HGB Concentration (g/dL) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Ery. Mean Corpuscular HGB Concentration (g/dL) <LLN ^[13]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[13] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	2	3		
Week 6	0	2		
Week 12	2	2		
Week 18	1	2		
Week 24	2	3		
Week 36	1	3		
Week 48	1	4		
Week 60	1	4		
Week 72	2	3		
Week 84	2	3		
Week 96	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Ery. Mean Corpuscular HGB (pg) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Ery. Mean Corpuscular HGB (pg) <LLN ^[14]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[14] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	1	3		
Week 6	1	2		
Week 12	1	2		
Week 18	1	2		
Week 24	1	2		
Week 36	1	2		
Week 48	1	3		
Week 60	0	3		
Week 72	0	3		
Week 84	0	3		
Week 96	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Ery. Mean Corpuscular Volume (fL) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Ery. Mean Corpuscular Volume (fL) <LLN ^[15]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[15] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	1	2		
Week 6	1	2		
Week 12	1	2		
Week 18	1	2		
Week 24	1	2		
Week 36	1	2		
Week 48	1	2		
Week 60	0	2		
Week 72	0	3		
Week 84	0	3		
Week 96	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Ery. Mean Corpuscular Volume (fL) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Ery. Mean Corpuscular Volume (fL) >ULN ^[16]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[16] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	0		
Week 48	0	0		
Week 60	0	0		
Week 72	0	0		
Week 84	1	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Erythrocytes ($10^{12}/L$) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Erythrocytes ($10^{12}/L$) <LLN ^[17]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[17] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	1	0		
Week 6	0	0		
Week 12	0	1		
Week 18	0	1		
Week 24	0	0		
Week 36	0	1		
Week 48	0	0		
Week 60	0	0		
Week 72	0	1		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Erythrocytes ($10^{12}/L$) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Erythrocytes ($10^{12}/L$) >ULN ^[18]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[18] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	1		
Week 6	0	0		
Week 12	0	1		
Week 18	0	0		
Week 24	1	2		
Week 36	0	2		
Week 48	0	1		
Week 60	0	1		
Week 72	0	2		
Week 84	0	1		
Week 96	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Hematocrit (%) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Hematocrit (%) <LLN ^[19]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[19] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	2	2		
Week 6	2	3		
Week 12	1	2		
Week 18	1	3		
Week 24	0	1		
Week 36	1	1		
Week 48	0	2		
Week 60	0	2		
Week 72	0	1		
Week 84	0	1		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Hemoglobin (g/dL) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Hemoglobin (g/dL) <LLN ^[20]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[20] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	2	3		
Week 6	2	3		
Week 12	1	3		
Week 18	1	3		
Week 24	0	2		
Week 36	1	3		
Week 48	1	3		
Week 60	0	3		
Week 72	0	3		
Week 84	0	3		
Week 96	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Leukocytes >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Leukocytes >ULN ^[21]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[21] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	0		
Week 48	0	1		
Week 60	0	0		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Lymphocytes/Leukocytes (%) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Lymphocytes/Leukocytes (%) <LLN ^[22]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[22] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	0		
Week 48	0	1		
Week 60	0	0		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Lymphocytes/Leukocytes (%) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Lymphocytes/Leukocytes (%) >ULN ^[23]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[23] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	1		
Week 6	0	1		
Week 12	0	1		
Week 18	0	1		
Week 24	0	1		
Week 36	0	1		
Week 48	0	1		
Week 60	0	1		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Monocytes/Leukocytes (%) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Monocytes/Leukocytes (%) >ULN ^[24]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[24] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	1		
Week 48	0	0		
Week 60	0	0		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Platelets ($10^9/L$) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Platelets ($10^9/L$) >ULN ^[25]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[25] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	1	0		
Week 6	0	1		
Week 12	0	0		
Week 18	0	0		
Week 24	0	1		
Week 36	0	0		
Week 48	0	0		
Week 60	0	0		
Week 72	0	1		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Blood Urea Nitrogen (mg/dL) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Blood Urea Nitrogen (mg/dL) <LLN ^[26]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[26] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	1	0		
Week 6	1	0		
Week 12	1	0		
Week 18	1	0		
Week 24	0	0		
Week 36	0	1		
Week 48	1	0		
Week 60	0	0		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Chloride (mmol/L) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Chloride (mmol/L) >ULN ^[27]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[27] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	1		
Week 6	0	1		
Week 12	0	0		
Week 18	0	1		
Week 24	0	0		
Week 36	0	1		
Week 48	0	0		
Week 60	0	1		
Week 72	0	1		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Creatine Kinase (U/L) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Creatine Kinase (U/L) >ULN ^[28]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[28] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	1	0		
Week 12	0	0		
Week 18	0	0		
Week 24	1	0		
Week 36	1	0		
Week 48	0	0		
Week 60	1	0		
Week 72	0	0		
Week 84	0	0		
Week 96	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Glucose (mg/dL) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Glucose (mg/dL) >ULN ^[29]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[29] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	1		
Week 24	0	0		
Week 36	0	0		
Week 48	0	0		
Week 60	0	0		
Week 72	0	0		
Week 84	0	1		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Lactate Dehydrogenase (U/L) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Lactate Dehydrogenase (U/L) <LLN ^[30]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[30] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	0		
Week 48	0	0		
Week 60	0	0		
Week 72	0	1		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Phosphate (mg/dL) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Phosphate (mg/dL) >ULN ^[31]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[31] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	1		
Week 24	0	0		
Week 36	0	0		
Week 48	0	0		
Week 60	0	0		
Week 72	0	1		
Week 84	0	1		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Protein (g/dL) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Protein (g/dL) >ULN ^[32]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[32] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	1		
Week 18	0	0		
Week 24	0	1		
Week 36	1	0		
Week 48	0	0		
Week 60	0	0		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Sodium (mmol/L) <LLN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Sodium (mmol/L) <LLN ^[33]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[33] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	2	0		
Week 6	1	0		
Week 12	0	0		
Week 18	3	1		
Week 24	0	1		
Week 36	0	0		
Week 48	0	1		
Week 60	0	0		
Week 72	0	1		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal serum laboratory values, Urate (mg/dL) >ULN

End point title	Safety and tolerability in terms of abnormal serum laboratory values, Urate (mg/dL) >ULN ^[34]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[34] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	1	0		
Week 6	1	1		
Week 12	1	0		
Week 18	1	1		
Week 24	1	1		
Week 36	1	1		
Week 48	1	1		
Week 60	1	1		
Week 72	1	1		
Week 84	1	1		
Week 96	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal urine laboratory values, Urine Ketones

End point title	Safety and tolerability in terms of abnormal urine laboratory values, Urine Ketones ^[35]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[35] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	1		
Week 24	0	0		
Week 36	0	0		
Week 48	0	1		
Week 60	0	0		
Week 72	0	0		
Week 84	0	0		
Week 96	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal urine laboratory values, Urine Occult Blood

End point title	Safety and tolerability in terms of abnormal urine laboratory values, Urine Occult Blood ^[36]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[36] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	1	1		
Week 6	2	1		
Week 12	1	2		
Week 18	1	1		
Week 24	1	1		
Week 36	1	1		
Week 48	1	1		
Week 60	1	1		
Week 72	2	1		
Week 84	1	1		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal urine laboratory values, Urine Protein

End point title	Safety and tolerability in terms of abnormal urine laboratory values, Urine Protein ^[37]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[37] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	2	1		
Week 6	1	1		
Week 12	2	1		
Week 18	1	0		
Week 24	2	1		
Week 36	2	0		
Week 48	1	1		
Week 60	3	1		
Week 72	3	1		
Week 84	2	1		
Week 96	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal ECG, abnormalities

End point title	Safety and tolerability in terms of abnormal ECG,
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[38] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 24	0	0		
Final Visit	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal physical exams, Cardiovascular

End point title	Safety and tolerability in terms of abnormal physical exams, Cardiovascular ^[39]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[39] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	1		
Week 48	0	1		
Week 60	0	1		
Week 72	0	1		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal physical exams, General Appearance

End point title	Safety and tolerability in terms of abnormal physical exams, General Appearance ^[40]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[40] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	1	2		
Week 6	1	2		
Week 12	1	2		
Week 18	1	2		
Week 24	1	2		
Week 36	1	2		
Week 48	1	2		
Week 60	1	2		
Week 72	1	2		
Week 84	1	2		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal physical exams, Head and Neck

End point title	Safety and tolerability in terms of abnormal physical exams, Head and Neck ^[41]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[41] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	1		
Week 6	0	1		
Week 12	0	1		
Week 18	0	1		
Week 24	0	1		
Week 36	0	1		
Week 48	0	1		
Week 60	0	1		
Week 72	0	1		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal physical exams, Musculoskeletal/Extremities

End point title	Safety and tolerability in terms of abnormal physical exams, Musculoskeletal/Extremities ^[42]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[42] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	0		
Week 48	0	1		
Week 60	0	0		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal physical exams, Skin

End point title	Safety and tolerability in terms of abnormal physical exams, Skin ^[43]
-----------------	---

End point description:

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

End point timeframe:

96 weeks

Notes:

[43] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	3	2		
Week 6	3	2		
Week 12	3	2		
Week 18	3	2		
Week 24	3	2		
Week 36	3	2		
Week 48	3	2		
Week 60	2	2		
Week 72	2	2		
Week 84	2	1		
Week 96	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability in terms of abnormal vital signs

End point title	Safety and tolerability in terms of abnormal vital signs ^[44]
-----------------	--

End point description:

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

End point timeframe:

96 weeks

Notes:

[44] - 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: There are no statistical analyses entered for primary endpoints. No formal hypothesis testing or analyses were done for safety endpoints.

End point values	Sequence A	Sequence B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: participants				
Baseline	0	0		
Week 6	0	0		
Week 12	0	0		
Week 18	0	0		
Week 24	0	0		
Week 36	0	0		
Week 48	0	0		
Week 60	0	0		
Week 72	0	0		
Week 84	0	0		
Week 96	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in LDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in LDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	--

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % LDL-C				
geometric mean (confidence interval 95%)				
Visit 1	-21 (-32.1 to -8)			
Visit 2	-18.6 (-28.4 to -7.4)			

Visit 3	-14.7 (-25.2 to -2.8)			
Visit 4	-12.1 (-23.8 to 1.4)			
Visit 5	-21.3 (-33.7 to -6.6)			
Visit 6	-20.5 (-33.6 to -4.8)			
Visit 7	-12.4 (-28.2 to 7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in HDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in HDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	--

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % HDL-C				
geometric mean (confidence interval 95%)				
Visit 1	12.3 (1.3 to 24.5)			
Visit 2	19 (6.2 to 33.4)			
Visit 3	5.2 (-8.4 to 20.8)			
Visit 4	4.4 (-10.8 to 22.2)			
Visit 5	4.4 (-12.7 to 24.9)			
Visit 6	9.4 (-9.4 to 32.1)			
Visit 7	3.8 (-13.1 to 23.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Total Cholesterol (TC) from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in Total Cholesterol (TC) from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	---

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % TC				
geometric mean (confidence interval 95%)				
Visit 1	-19.4 (-29.7 to -7.6)			
Visit 2	-16.8 (-25.7 to -6.8)			
Visit 3	-14 (-23.6 to -3.3)			
Visit 4	-11.8 (-22.3 to 0.1)			
Visit 5	-19.9 (-31.1 to -6.9)			
Visit 6	-18.3 (-30.2 to -4.3)			
Visit 7	-11.9 (-26.3 to 5.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Triglycerides (TG) from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in Triglycerides (TG) from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	---

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % TG				
geometric mean (confidence interval 95%)				
Visit 1	-17.3 (-31.9 to 0.5)			
Visit 2	-17.4 (-34.2 to 3.8)			
Visit 3	-16.2 (-36.1 to 10.1)			
Visit 4	-22 (-42.8 to 6.5)			
Visit 5	-23.3 (-45 to 7.1)			
Visit 6	-21.7 (-43.4 to 8.4)			
Visit 7	-28.5 (-47 to -3.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Non-HDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in Non-HDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	--

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % Non-HDL-C				
geometric mean (confidence interval 95%)				
Visit 1	-21.7 (-32.7 to -9)			
Visit 2	-19.2 (-28.8 to -8.3)			

Visit 3	-15.7 (-25.7 to -4.3)			
Visit 4	-13.3 (-24.3 to -0.7)			
Visit 5	-22.1 (-33.8 to -8.4)			
Visit 6	-21 (-33.2 to -6.5)			
Visit 7	-13.2 (-28.1 to 4.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in LDL-C/HDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in LDL-C/HDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	--

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % LDL-C/HDL-C				
geometric mean (confidence interval 95%)				
Visit 1	-39.4 (-51.6 to -24.1)			
Visit 2	-41.2 (-52.8 to -26.9)			
Visit 3	-36.1 (-48.8 to -20.2)			
Visit 4	-35 (-49.5 to -16.4)			
Visit 5	-48.6 (-61.3 to -31.7)			
Visit 6	-42.2 (-57.2 to -21.9)			
Visit 7	-27.8 (-47.4 to -0.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in TC/HDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in TC/HDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	---

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % TC/HDL-C				
geometric mean (confidence interval 95%)				
Visit 1	-30.6 (-38.3 to -21.9)			
Visit 2	-29.4 (-38.5 to -18.9)			
Visit 3	-20.5 (-32 to -7)			
Visit 4	-16.6 (-30.7 to 0.4)			
Visit 5	-24.1 (-38.6 to -6.2)			
Visit 6	-29.2 (-43.2 to -11.7)			
Visit 7	-15.6 (-33.7 to 7.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Non-HDL-C/HDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in Non-HDL-C/HDL-C from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	--

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % Non-HDL-C/HDL-C				
geometric mean (confidence interval 95%)				
Visit 1	-32.9 (-41.2 to -23.3)			
Visit 2	-31.5 (-41.2 to -20.3)			
Visit 3	-22.3 (-34.3 to -8.1)			
Visit 4	-18.1 (-32.8 to -0.3)			
Visit 5	-26.3 (-41.3 to -7.4)			
Visit 6	-31.8 (-46 to -13.9)			
Visit 7	-17.6 (-36.2 to 6.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in ApoB from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in ApoB from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	---

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % ApoB				
geometric mean (confidence interval 95%)				
Visit 1	-20.5 (-29.8 to -9.9)			
Visit 2	-18.7 (-26.7 to -9.8)			

Visit 3	-15.2 (-23.9 to -5.6)			
Visit 4	-10.5 (-20.4 to 0.5)			
Visit 5	-17.2 (-27.9 to -4.9)			
Visit 6	-19.2 (-30.2 to -6.5)			
Visit 7	-9.5 (-23.5 to 7.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in ApoA-1 from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in ApoA-1 from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	---

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % ApoA-1				
geometric mean (confidence interval 95%)				
Visit 1	8 (0 to 16.6)			
Visit 2	7 (-2.3 to 17.1)			
Visit 3	5.3 (-4.9 to 16.7)			
Visit 4	6.5 (-5.3 to 19.7)			
Visit 5	1 (-11.5 to 15.3)			
Visit 6	10.7 (-2.6 to 25.7)			
Visit 7	1.6 (-12.9 to 18.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in ApoB/ApoA-1 from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis

End point title	Percent change in ApoB/ApoA-1 from end of placebo of D3561C00005 to the end of D356NC00001, repeated measures analysis
-----------------	--

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: % ApoB/ApoA-1				
geometric mean (confidence interval 95%)				
Visit 1	-23.3 (-34.3 to -10.5)			
Visit 2	-22.1 (-32.7 to -9.8)			
Visit 3	-18.9 (-31.2 to -4.4)			
Visit 4	-15.7 (-30.2 to 1.7)			
Visit 5	-17 (-33.1 to 2.8)			
Visit 6	-26 (-41.1 to -7)			
Visit 7	-14.7 (-33.7 to 9.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic profile in terms of trough concentrations in pediatric HoFH taking a daily dose of rosuvastatin 40mg

End point title	Pharmacokinetic profile in terms of trough concentrations in pediatric HoFH taking a daily dose of rosuvastatin 40mg
-----------------	--

End point description:

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

End point timeframe:

Up to 22 months

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: ng/mL				
number (not applicable)				
Day 292	9			
Day 376	7.14			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

72 weeks

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

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19.0
--------------------	------

Reporting groups

Reporting group title	Overall
-----------------------	---------

Reporting group description:

All patients

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 9 (55.56%)		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		
Psychiatric disorders Attention deficit/hyperactivity disorder subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Otitis externa subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		

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

None reported