



Clinical trial results:

A double-blind, placebo-controlled, randomized study to evaluate the efficacy and safety of TAK-475 or placebo when co-administered with current lipid-lowering therapy in subjects with homozygous familial hypercholesterolemia

Summary

EudraCT number	2005-003626-26
Trial protocol	GB
Global end of trial date	04 May 2008

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	01-05-TL-475-016
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00263081
WHO universal trial number (UTN)	U1111-1122-7919

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	One Takeda Parkway, Deerfield, IL , United States, 60015
Public contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, trialdisclosures@takeda.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?	Yes
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	15 October 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 December 2006
Global end of trial reached?	Yes
Global end of trial date	04 May 2008
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the effect of TAK-475 QD compared to placebo on low-density lipoprotein cholesterol (LDL-C) in subjects with HoFH when co-administered with current lipid-lowering therapy for 12 weeks. This study was prematurely terminated since overall profile of the compound does not offer significant clinical advantage to patients over currently available lipid lowering agents.

Protection of trial subjects:

All participants signed an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	44
EEA total number of subjects	20

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)	6
Adults (18-64 years)	30
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 12 investigative sites in the United States, Canada, France, Poland, Netherlands, the United Kingdom, South Africa, and Israel from 22 November 2005 to 4 May 2008.

Pre-assignment

Screening details:

Participants with a diagnosis of homozygous familial hypercholesterolemia were enrolled equally in 1 of 23 treatment groups, once a day placebo, 50 mg or 100 mg or lapaquistat acetate (depending on participant screening body weight of <50 or >=50kg) followed by 50 mg or/ 100 mg lapaquistat acetate open label.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	lapaquistat acetate

Arm description:

Lapaquistat acetate, 50 or 100 mg based on body weight, orally, once daily, for 12 weeks, co-administered with the participant's current lipid lowering therapy.

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

Dosage and administration details:

lapaquistat acetate tablet

Arm title	Placebo
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Arm description:

Placebo matching lapaquistat acetate, tablets, orally, once daily, for 12 weeks, co-administered with the participant's current lipid lowering therapy

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

Dosage and administration details:

Placebo matching lapaquistat acetate

Number of subjects in period 1	lapaquistat acetate	Placebo
Started	23	21
Completed	23	21

Period 2

Period 2 title	Open-Label (OL) Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	lapaquistat acetate
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Arm description:

Lapaquistat acetate 50 or 100 mg based on body weight, tablets, orally, once daily, co-administered with the participant's current lipid lowering therapy during the open label treatment period.

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

Dosage and administration details:

lapaquistat acetate tablet

Number of subjects in period 2^[1]	lapaquistat acetate
Started	40
Completed	0
Not completed	40
Major Protocol Deviation	2
Study Termination	26
Adverse event, non-fatal	2
Voluntary Withdrawal	7
Other	2
Lost to follow-up	1

Notes:

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

Justification: 4 participants enrolled in the Double-blind Treatment Period of the study did not enter the Open Label Treatment Period of the study.

Baseline characteristics

Reporting groups

Reporting group title	lapaquistat acetate
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Reporting group description:

Lapaquistat acetate, 50 or 100 mg based on body weight, orally, once daily, for 12 weeks, co-administered with the participant's current lipid lowering therapy.

Reporting group title	Placebo
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Reporting group description:

Placebo matching lapaquistat acetate, tablets, orally, once daily, for 12 weeks, co-administered with the participant's current lipid lowering therapy

Reporting group values	lapaquistat acetate	Placebo	Total
Number of subjects	23	21	44
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)	4	3	7
Adolescents (12-17 years)	5	1	6
Adults (18-64 years)	13	17	30
From 65-84 years	1	0	1
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	24	28	
standard deviation	± 15.1	± 13.63	-
Gender categorical			
Units: Subjects			
Female	11	8	19
Male	12	13	25
Race			
Units: Subjects			
American Indian/Alaskan Native	1	2	3
Asian	0	1	1
Black/African American	2	0	2
White	20	18	38
Smoking Classification			
Units: Subjects			
Subject never smoked	19	16	35
Subject is a current smoker	2	5	7
Subject is a former smoker	2	0	2
Family History of Premature Coronary Heart Disease			
Units: Subjects			
Yes	13	12	25

No	9	8	17
Unknown	1	1	2
Genotypic Diagnosis of Homozygous Familial Hypercholesterolemia (HoFH) Confirmed at Baseline			
Units: Subjects			
Yes	21	19	40
No	2	2	4
Low-Density Lipoprotein Apheresis			
Units: Subjects			
Yes	17	13	30
No	6	8	14
Baseline Weight			
Units: Subjects			
<50 kg	6	5	11
≥50 kg	17	16	33
Height			
Units: cm			
arithmetic mean	161.9	162.5	-
standard deviation	± 14.08	± 15.08	-
Weight			
Units: kg			
arithmetic mean	61.71	65.3	-
standard deviation	± 20.1	± 25.38	-
Body Mass Index (BMI)			
Units: kg/m ²			
arithmetic mean	22.94	23.81	-
standard deviation	± 5.44	± 5.9	-

End points

End points reporting groups

Reporting group title	lapaquistat acetate
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Reporting group description:

Lapaquistat acetate, 50 or 100 mg based on body weight, orally, once daily, for 12 weeks, co-administered with the participant's current lipid lowering therapy.

Reporting group title	Placebo
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Reporting group description:

Placebo matching lapaquistat acetate, tablets, orally, once daily, for 12 weeks, co-administered with the participant's current lipid lowering therapy

Reporting group title	lapaquistat acetate
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Reporting group description:

Lapaquistat acetate 50 or 100 mg based on body weight, tablets, orally, once daily, co-administered with the participant's current lipid lowering therapy during the open label treatment period.

Primary: Percent Change from Baseline in Direct Low Density Lipoprotein Cholesterol

End point title	Percent Change from Baseline in Direct Low Density Lipoprotein Cholesterol
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End point description:

Fasting blood samples were collected and sent to a central laboratory for analysis of Direct Low Density Lipoprotein Cholesterol in millimoles/liter (mmol/L). The percent change was calculated as the value at Week 12 - Value at Baseline/Value at Baseline * 100. A negative percent change indicated improvement.

End point type	Primary
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End point timeframe:

Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: Percent change				
least squares mean (standard error)	-10.66 (\pm 3.769)	-3.59 (\pm 3.945)		

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis
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Comparison groups	lapaquistat acetate v Placebo
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Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.203 ^[1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.102
upper limit	3.971

Notes:

[1] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Percent Change from Baseline in Calculated Low Density Lipoprotein Cholesterol

End point title	Percent Change from Baseline in Calculated Low Density Lipoprotein Cholesterol
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End point description:

Fasting blood samples were collected and sent to a central laboratory for analysis of calculated Low Density Lipoprotein Cholesterol in millimoles/liter (mmol/L). The percent change was calculated as the value at Week 12 - Value at Baseline/Value at Baseline * 100. A negative percent change indicated improvement.

End point type	Secondary
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End point timeframe:

Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: Percent change				
least squares mean (standard error)	-11.27 (± 3.672)	-4.6 (± 3.843)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.217 ^[2]
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-6.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.419
upper limit	4.079

Notes:

[2] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Percent Change from Baseline in non- High Density Lipoprotein Cholesterol

End point title	Percent Change from Baseline in non- High Density Lipoprotein Cholesterol
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End point description:

Fasting blood samples were collected and sent to a central laboratory for analysis of non-High Density Lipoprotein Cholesterol in millimoles/liter (mmol/L). The percent change was calculated as the value at Week 12 - Value at Baseline/Value at Baseline * 100. A negative percent change indicated improvement.

End point type	Secondary
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End point timeframe:

Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: Percent change				
least squares mean (standard error)	-11.11 (\pm 3.62)	-3.9 (\pm 3.789)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.177 [3]
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-7.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.809
upper limit	3.39

Notes:

[3] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Percent Change from Baseline in Triglycerides

End point title	Percent Change from Baseline in Triglycerides
End point description:	Fasting blood samples were collected and sent to a central laboratory for analysis of Triglycerides in millimoles/liter (mmol/). The percent change was calculated as the value at Week 12/Value at Baseline * 100. A negative percent change indicated improvement.
End point type	Secondary
End point timeframe:	Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: Percent change				
least squares mean (standard error)	-5.203 (\pm 6.5399)	9.242 (\pm 6.8454)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.135 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-14.446
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.6
upper limit	4.709

Notes:

[4] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Percent Change from Baseline in Total Cholesterol

End point title	Percent Change from Baseline in Total Cholesterol
End point description:	Fasting blood samples were collected and sent to a central laboratory for analysis of Total Cholesterol in millimoles/liter (mmol/L). The percent change was calculated as the value at Week 12 - Value at Baseline/Value at Baseline * 100. A negative percent change indicated improvement.
End point type	Secondary

End point timeframe:

Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: Percent change				
least squares mean (standard error)	-10.01 (\pm 3.348)	-3.39 (\pm 3.504)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.615
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.418
upper limit	3.187

Notes:

[5] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Percent Change from Baseline in High Density Lipoprotein Cholesterol

End point title	Percent Change from Baseline in High Density Lipoprotein Cholesterol
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End point description:

Fasting blood samples were collected and sent to a central laboratory for analysis of High Density Lipoprotein Cholesterol in millimoles/liter (mmol/L). The percent change was calculated as the value at Week 12 - Value at Baseline/Value at Baseline * 100. A negative percent change indicated improvement.

End point type	Secondary
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End point timeframe:

Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: Percent change				
least squares mean (standard error)	-4.97 (± 2.712)	2.28 (± 2.838)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072 [6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.248
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.178
upper limit	0.681

Notes:

[6] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Percent Change from Baseline in Very Low Density Lipoprotein Cholesterol

End point title	Percent Change from Baseline in Very Low Density Lipoprotein Cholesterol
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End point description:

Fasting blood samples were collected and sent to a central laboratory for analysis of Very Low Density Lipoprotein Cholesterol in millimoles/liter (mmol/L). The percent change was calculated as the value at Week 12 - Value at Baseline/Value at Baseline * 100. A negative percent change indicated improvement.

End point type	Secondary
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End point timeframe:

Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: Percent change				
least squares mean (standard error)	-4.88 (± 6.826)	9.61 (± 7.145)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.151 [7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-14.495
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.488
upper limit	5.497

Notes:

[7] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Percent Change from Baseline in Apolipoprotein A1

End point title	Percent Change from Baseline in Apolipoprotein A1
End point description:	Fasting blood samples were collected and sent to a central laboratory for analysis of Apolipoprotein A1 in milligrams/deciliter (mg/dL). The percent change was calculated as the value at Week 12/Value at Baseline * 100. A negative percent change indicated improvement.
End point type	Secondary
End point timeframe:	Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: mg/dL				
least squares mean (standard error)	-2.68 (± 3.048)	0.04 (± 3.191)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.541 [8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.65
upper limit	6.2

Notes:

[8] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Percent Change from Baseline in Apolipoprotein B

End point title	Percent Change from Baseline in Apolipoprotein B
End point description:	Fasting blood samples were collected and sent to a central laboratory for analysis of Apolipoprotein B in milligrams/deciliter (mg/dL). The percent change was calculated as the value at Week 12 - Value at Baseline/Value at Baseline * 100. A negative percent change indicated improvement.
End point type	Secondary
End point timeframe:	Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: Percent change				
least squares mean (standard error)	-8.59 (± 3.379)	-3.97 (± 3.536)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35 [9]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.51
upper limit	5.26

Notes:

[9] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Change from Baseline in the Ratio of Low Density Lipoprotein Cholesterol (LDL-C)/High Density Lipoprotein Cholesterol (HDL-C)

End point title	Change from Baseline in the Ratio of Low Density Lipoprotein Cholesterol (LDL-C)/High Density Lipoprotein Cholesterol (HDL-C)
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End point description:

Fasting blood samples were collected and sent to a central laboratory for analysis of LDL-C and HDL-C. The ratio of LDL-C/HDL-C was calculated.

End point type	Secondary
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End point timeframe:

Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: mmol/L				
least squares mean (standard error)	-0.13 (± 0.53)	-0.65 (± 0.555)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.504 ^[10]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.518
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.033
upper limit	2.068

Notes:

[10] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Change from Baseline in the Ratio of Total Cholesterol (TC)/High Density Lipoprotein Cholesterol (HDL-C)

End point title	Change from Baseline in the Ratio of Total Cholesterol (TC)/High Density Lipoprotein Cholesterol (HDL-C)
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End point description:

Fasting blood samples were collected and sent to a central laboratory for analysis of Total Cholesterol and HDL-C.. The ratio of Total Cholesterol/HDL-C was calculated.

End point type	Secondary
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End point timeframe:

Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: mmol/L				
least squares mean (standard error)	-0.19 (\pm 0.528)	-0.72 (\pm 0.553)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.491 ^[11]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.532
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.014
upper limit	2.077

Notes:

[11] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Secondary: Change from Baseline in the Ratio of Apolipoprotein B/Apolipoprotein A1

End point title	Change from Baseline in the Ratio of Apolipoprotein B/Apolipoprotein A1
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End point description:

Fasting blood samples were collected and sent to a central laboratory for analysis of Apolipoprotein A1 and Apolipoprotein B. The ratio of Apolipoprotein B/Apolipoprotein A1 was calculated.

End point type	Secondary
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End point timeframe:

Baseline and Week 12 or Final Visit

End point values	lapaquistat acetate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: mg/dL				
least squares mean (standard error)	-0.09 (± 0.109)	-0.09 (± 0.114)		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	lapaquistat acetate v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.975 ^[12]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.324
upper limit	0.314

Notes:

[12] - Analysis of covariance (ANCOVA) model with terms for treatment effect and baseline value (as covariate).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of double-blind study drug and no more than 30 days after the last dose of study drug (up to 73 weeks).

Adverse event reporting additional description:

Due to the design of the study, the most common ($\geq 5\%$) non-serious adverse events were determined separately for each period of the study, the Double Blind period and the Open Label period. A result of 0 in a column means that the event did not meet the $\geq 5\%$ threshold for that study period but did meet the threshold for the other study period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	lapaquistat acetate
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Reporting group description:

Lapaquistat acetate, 50 or 100 mg based on body weight, orally, once daily, for 12 weeks, co-administered with the participant's current lipid lowering therapy.

Reporting group title	Placebo
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Reporting group description:

Placebo matching lapaquistat acetate, tablets, orally, once daily, for 12 weeks, co-administered with the participant's current lipid lowering therapy

Reporting group title	Lapaquistat acetate 50 mg _OL
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Reporting group description:

Lapaquistat acetate, 50 mg based on body weight, orally, once daily, co-administered with the participant's current lipid lowering therapy in the open-label (OL) treatment period.

Reporting group title	Lapaquistat acetate 100 mg _OL
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Reporting group description:

Lapaquistat acetate, 100 mg based on body weight, orally, once daily, co-administered with the participant's current lipid lowering therapy in the open-label (OL) treatment period.

Serious adverse events	lapaquistat acetate	Placebo	Lapaquistat acetate 50 mg _OL
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 23 (8.70%)	1 / 21 (4.76%)	1 / 10 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leiomyoma			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Aortic stenosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (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
Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (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
Atrial flutter			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (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
Cardiac tamponade			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cystitis			

subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Lapaquistat acetate 100 mg _OL		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 30 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leiomyoma			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac tamponade			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	lapaquistat acetate	Placebo	Lapaquistat acetate 50 mg _OL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 23 (30.43%)	10 / 21 (47.62%)	8 / 10 (80.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Xanthoma subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	1 / 10 (10.00%) 1
Vascular disorders Aortic stenosis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	1 / 10 (10.00%) 1
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0 0 / 23 (0.00%) 0 0 / 23 (0.00%) 0	0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0	1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	1 / 10 (10.00%) 1
Respiratory, thoracic and mediastinal disorders Pharyngolaryngeal pain subjects affected / exposed occurrences (all) Wheezing subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0 0 / 23 (0.00%) 0	0 / 21 (0.00%) 0 0 / 21 (0.00%) 0	1 / 10 (10.00%) 1 1 / 10 (10.00%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	1 / 10 (10.00%) 1
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	0 / 10 (0.00%) 0

increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Red blood cells urine			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram abnormal			
subjects affected / exposed	0 / 23 (0.00%)	2 / 21 (9.52%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 23 (8.70%)	2 / 21 (9.52%)	1 / 10 (10.00%)
occurrences (all)	3	2	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 23 (4.35%)	4 / 21 (19.05%)	1 / 10 (10.00%)
occurrences (all)	1	5	1
Constipation			

subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	1 / 10 (10.00%) 1
Diarrhoea subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	0 / 10 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	0 / 10 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	0 / 10 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 5	2 / 21 (9.52%) 2	2 / 10 (20.00%) 4
Nausea subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 5	0 / 21 (0.00%) 0	0 / 10 (0.00%) 0
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	2 / 10 (20.00%) 2
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	1 / 10 (10.00%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	0 / 10 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	0 / 10 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 21 (0.00%) 0	0 / 10 (0.00%) 0
Musculoskeletal pain			

subjects affected / exposed	2 / 23 (8.70%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Neck pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	2 / 23 (8.70%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	4	0	1
Tendonitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Erythema infectiosum			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	3
Pharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	4
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Iron deficiency			
subjects affected / exposed	0 / 23 (0.00%)	2 / 21 (9.52%)	1 / 10 (10.00%)
occurrences (all)	0	2	1

Non-serious adverse events

Lapaquistat acetate
100 mg _OL

Total subjects affected by non-serious adverse events subjects affected / exposed	23 / 30 (76.67%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Xanthoma subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Vascular disorders Aortic stenosis subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Pharyngolaryngeal pain subjects affected / exposed occurrences (all) Wheezing subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1 0 / 30 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Red blood cells urine subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Transaminases increased subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 5		
Electrocardiogram abnormal subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Injury, poisoning and procedural complications Muscle strain subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Procedural pain subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3		
Cardiac disorders Aortic valve incompetence subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Constipation subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Dyspepsia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Toothache subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Vomiting subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Nausea subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 5		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 6		
Muscle spasms subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3		

Musculoskeletal chest pain subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Neck pain subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 4		
Tendonitis subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Infections and infestations			
Cystitis subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Erythema infectiosum subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 5		
Pharyngitis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Metabolism and nutrition disorders			
Dehydration subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Iron deficiency			

subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2006	Amendment 2: For Poland Only: Changed age minimum from 8 to 12 years.
13 December 2007	Amendment 3: Dose reductions of lapaquistat acetate. Participants taking 100 mg reduced to 50 mg. Participants taking 50 mg (Less than 50 kg) were no longer allowed to participate in the study because a lower dose was not available.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 December 2007	Interruption in dosing with lapaquistat acetate until Protocol Amendment 3 was approved and the revised ICF was signed.	-

Notes:

Limitations and caveats

None reported