Clinical trial results:
A dose finding study to assess the safety and efficacy of K-877 in patients with statin-controlled LDL-C but abnormal lipid levels

Summary

EudraCT number	2013-001517-32
Trial protocol	SE GB HU DE CZ NL DK PL
Global end of trial date	23 September 2014

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	01 April 2016

Trial information

Trial identification

Sponsor protocol code	K-877-201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Kowa Research Europe Ltd
Sponsor organisation address	105 Wharfedale Road, Winnersh Triangle, Wokingham, United Kingdom, RG41 5RB
Public contact	Regulatory Affairs, Kowa Research Europe Ltd, +44 0118 922 9000,
Scientific contact	Regulatory Affairs, Kowa Research Europe Ltd, +44 0118 922 9000,

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	20 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2014
Global end of trial reached?	Yes
Global end of trial date	23 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the dose response of the following parameters:
•% change in non-high-density lipoprotein cholesterol (non-HDL-C) from baseline to Week 12
•% change in TG from baseline to Week 12

To assess the safety and tolerability of K-877 in patients with residual cardiovascular risk despite statin-controlled low density lipoprotein (LDL-C) concentration as particularly evaluated by:
•Change and % change in serum creatinine from baseline to Week 12
•Change and % change in log(homocysteine) from baseline to Week 12

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. Each patient was assured of his/her right to withdraw from the study at any time. Close monitoring of all subjects was adhered to throughout the trial conduct.
Throughout the study, patients were not allowed to change the dose, dosing regimen (e.g. morning or evening dose), or the type of statin and encouraged to continue on the same diet and exercise regimen. In general, any other medication not excluded by the protocol was permitted.

Background therapy:

Stable statin therapy (except for pravastatin, lovastatin, and fluvastatin)

Evidence for comparator: -

Actual start date of recruitment	11 October 2013
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	Poland: 31
Country: Number of subjects enrolled	Netherlands: 56
Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	Denmark: 34
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 93
Country: Number of subjects enrolled	Russian Federation: 116
Worldwide total number of subjects	408
EEA total number of subjects	292

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	273
From 65 to 84 years	135
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The Screening Period was up to a maximum of 4 weeks in duration and consisted of 1 or 2 visits: Screening Visit (SV) 1 for all patients, and SV 2 for patients who failed to meet inclusion criterion #5 (fasting TG ≥175 mg/dL [1.97 mmol/L] and ≤500 mg/dL [5.65 mmol/L]) at SV 1.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo twice daily

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Two placebo tablets were to be taken orally, twice daily in the morning and the evening. Duration of treatment was 12 weeks.

Arm title	K-877 0.05 mg twice daily

Arm description: -

Arm type	Experimental
Investigational medicinal product name	K-877 0.05 mg tablet
Investigational medicinal product code	K-877
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One K-877 0.05 mg tablet and one placebo tablet were to be taken orally, twice daily in the morning and the evening. Duration of treatment was 12 weeks.

Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One K-877 0.05 mg tablet and one placebo tablet were to be taken orally, twice daily in the morning and the evening. Duration of treatment was 12 weeks.

Arm title	K-877 0.1 mg twice daily

Arm description: -

Arm type	Experimental

Investigational medicinal product name	K-877 0.1 mg tablet
Investigational medicinal product code	K-877
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One K-877 0.1 mg tablet and one placebo tablet were to be taken orally, twice daily in the morning and the evening. Duration of treatment was 12 weeks.

Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One K-877 0.1 mg tablet and one placebo tablet were to be taken orally, twice daily in the morning and the evening. Duration of treatment was 12 weeks.

Arm title	K-877 0.2 mg twice daily

Arm description: -

Arm type	Experimental
Investigational medicinal product name	K-877 0.2 mg tablet
Investigational medicinal product code	K-877
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One K-877 0.2 mg tablet and one placebo tablet were to be taken orally, twice daily in the morning and the evening. Duration of treatment was 12 weeks.

Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One K-877 0.2 mg tablet and one placebo tablet were to be taken orally, twice daily in the morning and the evening. Duration of treatment was 12 weeks.

Arm title	K-877 0.1 mg once daily

Arm description: -

Arm type	Experimental
Investigational medicinal product name	K-877 0.05 mg tablet
Investigational medicinal product code	K-877
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Two K-877 0.05 mg tablets were to be taken orally in the morning and two placebo tablets were to be taken orally in the evening. Duration of treatment was 12 weeks.

Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Two K-877 0.05 mg tablets were to be taken orally in the morning and two placebo tablets were to be

taken orally in the evening. Duration of treatment was 12 weeks.

Arm title	K-877 0.2 mg once daily
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	K-877 0.1 mg tablet
Investigational medicinal product code	K-877
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Two K-877 0.1 mg tablets were to be taken orally in the morning and two placebo tablets were to be taken orally in the evening. Duration of treatment was 12 weeks.

Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Two K-877 0.1 mg tablets were to be taken orally in the morning and two placebo tablets were to be taken orally in the evening. Duration of treatment was 12 weeks.

Arm title	K-877 0.4 mg once daily
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	K-877 0.2 mg tablet
Investigational medicinal product code	K-877
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Two K-877 0.2 mg tablets were to be taken orally in the morning and two placebo tablets were to be taken orally in the evening. Duration of treatment was 12 weeks.

Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Two K-877 0.2 mg tablets were to be taken orally in the morning and two placebo tablets were to be taken orally in the evening. Duration of treatment was 12 weeks.

Number of subjects in period 1	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily
Started	60	58	58
Completed	55	54	50
Not completed	5	4	8
Consent withdrawn by subject	3	4	3
Adverse event, non-fatal	1	-	2
Lost to follow-up	-	-	2
Protocol deviation	1	-	1

Number of subjects in period 1	K-877 0.2 mg twice daily	K-877 0.1 mg once daily	K-877 0.2 mg once daily
Started	57	58	58
Completed	52	54	56
Not completed	5	4	2
Consent withdrawn by subject	2	2	1
Adverse event, non-fatal	3	2	1
Lost to follow-up	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	K-877 0.4 mg once daily
Started	59
Completed	54
Not completed	5
Consent withdrawn by subject	3
Adverse event, non-fatal	1
Lost to follow-up	-
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo twice daily
Reporting group description: -	
Reporting group title	K-877 0.05 mg twice daily
Reporting group description: -	
Reporting group title	K-877 0.1 mg twice daily
Reporting group description: -	
Reporting group title	K-877 0.2 mg twice daily
Reporting group description: -	
Reporting group title	K-877 0.1 mg once daily
Reporting group description: -	
Reporting group title	K-877 0.2 mg once daily
Reporting group description: -	
Reporting group title	K-877 0.4 mg once daily
Reporting group description: -	

Reporting group values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily
Number of subjects	60	58	58
Age categorical Units: Subjects			
Adults (18-64 years)	38	39	40
From 65-84 years	22	19	18
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	61	59	58
standard deviation	± 10.3	± 9.8	± 12.3
Gender categorical Units: Subjects			
Female	17	18	18
Male	43	40	40

Reporting group values	K-877 0.2 mg twice daily	K-877 0.1 mg once daily	K-877 0.2 mg once daily
Number of subjects	57	58	58
Age categorical Units: Subjects			
Adults (18-64 years)	37	43	37
From 65-84 years	20	15	21
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	61	57	59
standard deviation	± 8.9	± 9.7	± 11.7
Gender categorical Units: Subjects			
Female	17	24	18

Male	40	34	40

Reporting group values	K-877 0.4 mg once daily	Total	
Number of subjects	59	408	
Age categorical Units: Subjects			
Adults (18-64 years)	39	273	
From 65-84 years	20	135	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	59		
standard deviation	± 9.7	-	
Gender categorical Units: Subjects			
Female	14	126	
Male	45	282	

End points

End points reporting groups	
Reporting group title	Placebo twice daily
Reporting group description: -	
Reporting group title	K-877 0.05 mg twice daily
Reporting group description: -	
Reporting group title	K-877 0.1 mg twice daily
Reporting group description: -	
Reporting group title	K-877 0.2 mg twice daily
Reporting group description: -	
Reporting group title	K-877 0.1 mg once daily
Reporting group description: -	
Reporting group title	K-877 0.2 mg once daily
Reporting group description: -	
Reporting group title	K-877 0.4 mg once daily
Reporting group description: -	

Primary: Percent change in TG	
End point title	Percent change in TG
End point description:	
End point type	Primary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	52	50	49
Units: percent				
least squares mean (standard error)	15 (± 4.85)	-21.2 (± 4.96)	-30.8 (± 5.08)	-39.5 (± 5.11)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	52	52	
Units: percent				
least squares mean (standard error)	-19.1 (± 4.98)	-22.7 (± 4.88)	-27.7 (± 4.99)	

Statistical analyses

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.05 mg twice daily
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-36.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.5
upper limit	-18.7
Variability estimate	Standard error of the mean
Dispersion value	6.72

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-45.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.4
upper limit	-28.2
Variability estimate	Standard error of the mean
Dispersion value	6.81

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-54.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-72.1
upper limit	-36.8
Variability estimate	Standard error of the mean
Dispersion value	6.83

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.5
upper limit	-16.6
Variability estimate	Standard error of the mean
Dispersion value	6.76

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-37.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55
upper limit	-20.3
Variability estimate	Standard error of the mean
Dispersion value	6.72

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-42.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.1
upper limit	-25.3
Variability estimate	Standard error of the mean
Dispersion value	6.75

Primary: Percent change in non-HDL-C

End point title	Percent change in non-HDL-C
End point description:	
End point type	Primary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	52	50	49
Units: percent				
least squares mean (standard error)	2.1 (± 2.9)	-4.8 (± 2.98)	-5.4 (± 3.04)	-6.8 (± 3.05)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	52	52	
Units: percent				
least squares mean (standard error)	-3.2 (± 2.96)	-7.1 (± 2.88)	-5.7 (± 2.99)	

Statistical analyses

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.05 mg twice daily

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.307
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.8
upper limit	3.2
Variability estimate	Standard error of the mean
Dispersion value	3.87

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.237
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.5
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	3.91

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	1.3

Variability estimate	Standard error of the mean
Dispersion value	3.91

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.3
upper limit	4.8
Variability estimate	Standard error of the mean
Dispersion value	3.88

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.086
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.1
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	3.85

Statistical analysis title	Dunnett's Test in MMRM Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.187
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	2.2
Variability estimate	Standard error of the mean
Dispersion value	3.87

Primary: Percent change in serum creatinine

End point title	Percent change in serum creatinine
End point description:	
End point type	Primary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	56	54	54
Units: percent				
least squares mean (standard error)	1.13 (± 1.41)	1.53 (± 1.43)	1.82 (± 1.46)	4.92 (± 1.46)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	56	
Units: percent				
least squares mean (standard error)	1.15 (± 1.4)	3.02 (± 1.36)	3.56 (± 1.43)	

Statistical analyses

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.05 mg twice daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.824
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	4.01
Variability estimate	Standard error of the mean
Dispersion value	1.83

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.706
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.94
upper limit	4.34
Variability estimate	Standard error of the mean
Dispersion value	1.85

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	7.43

Variability estimate	Standard error of the mean
Dispersion value	1.85

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.989
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.55
upper limit	3.6
Variability estimate	Standard error of the mean
Dispersion value	1.82

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.297
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	5.46
Variability estimate	Standard error of the mean
Dispersion value	1.81

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.185
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	6.05
Variability estimate	Standard error of the mean
Dispersion value	1.84

Primary: Percent change in Log(Homocysteine)

End point title	Percent change in Log(Homocysteine)
End point description:	
End point type	Primary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	56	54	54
Units: percent				
least squares mean (standard error)	3 (± 1.14)	2.9 (± 1.16)	5.89 (± 1.18)	8.45 (± 1.18)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	56	
Units: percent				
least squares mean (standard error)	3.93 (± 1.13)	5.91 (± 1.1)	8.37 (± 1.15)	

Statistical analyses

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.05 mg twice daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.948
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.01
upper limit	2.82
Variability estimate	Standard error of the mean
Dispersion value	1.48

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	5.82
Variability estimate	Standard error of the mean
Dispersion value	1.49

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.51
upper limit	8.39

Variability estimate	Standard error of the mean
Dispersion value	1.49

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.529
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.97
upper limit	3.82
Variability estimate	Standard error of the mean
Dispersion value	1.47

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	5.8
Variability estimate	Standard error of the mean
Dispersion value	1.47

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.46
upper limit	8.28
Variability estimate	Standard error of the mean
Dispersion value	1.48

Secondary: Percent change in HDL-C

End point title	Percent change in HDL-C
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	56	54	54
Units: percent				
least squares mean (standard error)	-0.05 (± 2.69)	7.59 (± 2.73)	12.84 (± 2.8)	10.89 (± 2.78)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	56	
Units: percent				
least squares mean (standard error)	3.66 (± 2.66)	10.32 (± 2.6)	7.29 (± 2.73)	

Statistical analyses

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.05 mg twice daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	14.53
Variability estimate	Standard error of the mean
Dispersion value	3.5

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	12.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.94
upper limit	19.84
Variability estimate	Standard error of the mean
Dispersion value	3.53

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	10.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.01
upper limit	17.88

Variability estimate	Standard error of the mean
Dispersion value	3.53

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.286
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.12
upper limit	10.55
Variability estimate	Standard error of the mean
Dispersion value	3.48

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	10.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.55
upper limit	17.2
Variability estimate	Standard error of the mean
Dispersion value	3.47

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	14.22
Variability estimate	Standard error of the mean
Dispersion value	3.5

Secondary: Percent change in total cholesterol

End point title	Percent change in total cholesterol
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	56	54	54
Units: percent				
least squares mean (standard error)	0.65 (± 2.1)	-1.42 (± 2.12)	-1.99 (± 2.17)	-3.13 (± 2.17)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	56	
Units: percent				
least squares mean (standard error)	-1.67 (± 2.07)	-2.12 (± 2.02)	-1.68 (± 2.12)	

Statistical analyses

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.05 mg twice daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.446
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.43
upper limit	3.28
Variability estimate	Standard error of the mean
Dispersion value	2.72

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.338
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.05
upper limit	2.77
Variability estimate	Standard error of the mean
Dispersion value	2.75

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.169
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.19
upper limit	1.62

Variability estimate	Standard error of the mean
Dispersion value	2.75

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.392
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.64
upper limit	3
Variability estimate	Standard error of the mean
Dispersion value	2.71

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.306
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.07
upper limit	2.54
Variability estimate	Standard error of the mean
Dispersion value	2.7

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.393
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.68
upper limit	3.02
Variability estimate	Standard error of the mean
Dispersion value	2.72

Secondary: Percent change in Remnant Cholesterol

End point title	Percent change in Remnant Cholesterol
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	56	54	54
Units: percent				
least squares mean (standard error)	22.25 (± 6.08)	-13.3 (± 6.16)	-26.6 (± 6.3)	-35.8 (± 6.29)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	56	
Units: percent				
least squares mean (standard error)	-17.6 (± 6.01)	-23.6 (± 5.87)	-23.2 (± 6.18)	

Statistical analyses

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.05 mg twice daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-35.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.1
upper limit	-20
Variability estimate	Standard error of the mean
Dispersion value	7.89

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-48.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64.5
upper limit	-33.1
Variability estimate	Standard error of the mean
Dispersion value	7.98

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-73.7
upper limit	-42.4

Variability estimate	Standard error of the mean
Dispersion value	7.97

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-39.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.3
upper limit	-24.4
Variability estimate	Standard error of the mean
Dispersion value	7.84

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-45.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.2
upper limit	-30.5
Variability estimate	Standard error of the mean
Dispersion value	7.82

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-45.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.1
upper limit	-29.9
Variability estimate	Standard error of the mean
Dispersion value	7.93

Secondary: Percent change in LDL-C

End point title	Percent change in LDL-C
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	56	54	54
Units: percent				
least squares mean (standard error)	-3.01 (± 3.56)	5 (± 3.61)	13.06 (± 3.68)	17.49 (± 3.7)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	56	
Units: percent				
least squares mean (standard error)	6.18 (± 3.52)	8.21 (± 3.43)	12.65 (± 3.62)	

Statistical analyses

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.05 mg twice daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.084
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	8.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	17.1
Variability estimate	Standard error of the mean
Dispersion value	4.62

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	16.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.88
upper limit	25.24
Variability estimate	Standard error of the mean
Dispersion value	4.67

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	20.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.3
upper limit	29.68

Variability estimate	Standard error of the mean
Dispersion value	4.67

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	18.22
Variability estimate	Standard error of the mean
Dispersion value	4.59

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.21
upper limit	20.22
Variability estimate	Standard error of the mean
Dispersion value	4.58

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	15.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.55
upper limit	24.77
Variability estimate	Standard error of the mean
Dispersion value	4.63

Secondary: Percent change in apolipoprotein A1

End point title	Percent change in apolipoprotein A1
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	56	54	52
Units: percent				
least squares mean (standard error)	1.82 (± 1.9)	6.25 (± 1.93)	4.78 (± 1.97)	2.23 (± 1.99)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	57	56	
Units: percent				
least squares mean (standard error)	1.72 (± 1.88)	3.71 (± 1.86)	4.47 (± 1.93)	

Statistical analyses

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.05 mg twice daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	9.28
Variability estimate	Standard error of the mean
Dispersion value	2.47

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.234
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.93
upper limit	7.86
Variability estimate	Standard error of the mean
Dispersion value	2.49

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.871
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.53
upper limit	5.35

Variability estimate	Standard error of the mean
Dispersion value	2.51

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.969
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.92
upper limit	4.73
Variability estimate	Standard error of the mean
Dispersion value	2.45

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.441
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.94
upper limit	6.74
Variability estimate	Standard error of the mean
Dispersion value	2.46

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.284
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	7.5
Variability estimate	Standard error of the mean
Dispersion value	2.47

Secondary: Percent change in apolipoprotein B

End point title	Percent change in apolipoprotein B
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	56	54	52
Units: percent				
least squares mean (standard error)	0.48 (± 2.94)	2.2 (± 2.99)	-0.23 (± 3.05)	-2.71 (± 3.1)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	57	56	
Units: percent				
least squares mean (standard error)	-1.62 (± 2.91)	-0.57 (± 2.87)	-0.89 (± 2.98)	

Statistical analyses

Statistical analysis title	ANCOVA Analysis
Comparison groups	K-877 0.05 mg twice daily v Placebo twice daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.653
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.81
upper limit	9.25
Variability estimate	Standard error of the mean
Dispersion value	3.83

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.855
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	6.89
Variability estimate	Standard error of the mean
Dispersion value	3.86

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.415
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	4.5

Variability estimate	Standard error of the mean
Dispersion value	3.91

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.57
upper limit	5.38
Variability estimate	Standard error of the mean
Dispersion value	3.8

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.783
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.53
upper limit	6.43
Variability estimate	Standard error of the mean
Dispersion value	3.8

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.721
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9
upper limit	6.16
Variability estimate	Standard error of the mean
Dispersion value	3.83

Secondary: Percent change in apolipoprotein C3

End point title	Percent change in apolipoprotein C3
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to Week 12	

End point values	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily	K-877 0.2 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	56	54	52
Units: percent				
least squares mean (standard error)	5.13 (± 3.85)	-10.3 (± 3.9)	-23.6 (± 3.98)	-30.8 (± 4.04)

End point values	K-877 0.1 mg once daily	K-877 0.2 mg once daily	K-877 0.4 mg once daily	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	57	56	
Units: percent				
least squares mean (standard error)	-12 (± 3.82)	-19.2 (± 3.75)	-18.6 (± 3.92)	

Statistical analyses

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.05 mg twice daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-15.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.3
upper limit	-5.63
Variability estimate	Standard error of the mean
Dispersion value	5

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg twice daily
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-28.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.6
upper limit	-18.8
Variability estimate	Standard error of the mean
Dispersion value	5.05

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg twice daily
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46
upper limit	-25.9

Variability estimate	Standard error of the mean
Dispersion value	5.1

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.1 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-17.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.9
upper limit	-7.28
Variability estimate	Standard error of the mean
Dispersion value	4.99

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.2 mg once daily
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-24.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.1
upper limit	-14.6
Variability estimate	Standard error of the mean
Dispersion value	4.97

Statistical analysis title	ANCOVA Analysis
Comparison groups	Placebo twice daily v K-877 0.4 mg once daily

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-23.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.6
upper limit	-13.9
Variability estimate	Standard error of the mean
Dispersion value	5.01

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were to be reported from signing of the Informed Consent Form until the last study visit. Serious adverse events were to be collected from signing of the Informed Consent Form until 30 days after the last dose of study medication.

Adverse event reporting additional description:

Only treatment-emergent adverse events (i.e. events not present prior to the initiation of the study drugs or events already present that worsens in either intensity or frequency following exposure to the study drugs) are summerised here.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo twice daily
Reporting group description: -	
Reporting group title	K-877 0.05 mg twice daily
Reporting group description: -	
Reporting group title	K-877 0.1 mg twice daily
Reporting group description: -	
Reporting group title	K-877 0.2 mg twice daily
Reporting group description: -	
Reporting group title	K-877 0.1 mg once daily
Reporting group description: -	
Reporting group title	K-877 0.2 mg once daily
Reporting group description: -	
Reporting group title	K-877 0.4 mg once daily

Reporting group description: -

Serious adverse events	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	1 / 58 (1.72%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal polyp			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Lung cancer metastatic			

subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	0 / 58 (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			
Arrhythmia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Cardiovascular insufficiency			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	0 / 58 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	K-877 0.2 mg twice daily	K-877 0.1 mg once daily	K-877 0.2 mg once daily
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 57 (1.75%)	3 / 58 (5.17%)	2 / 58 (3.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal polyp			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 58 (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
Lung cancer metastatic			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 58 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 58 (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
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 58 (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
Cardiovascular insufficiency			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			

subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 58 (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			
Appendicitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	K-877 0.4 mg once daily		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 59 (3.39%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal polyp			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung cancer metastatic			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiovascular insufficiency			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 59 (1.69%)		
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	Placebo twice daily	K-877 0.05 mg twice daily	K-877 0.1 mg twice daily
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 60 (56.67%)	29 / 57 (50.88%)	21 / 58 (36.21%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 57 (0.00%)	1 / 58 (1.72%)
occurrences (all)	2	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 60 (3.33%)	0 / 57 (0.00%)	2 / 58 (3.45%)
occurrences (all)	2	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 60 (8.33%)	1 / 57 (1.75%)	0 / 58 (0.00%)
occurrences (all)	5	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	3
Back pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 60 (5.00%)	1 / 57 (1.75%)	1 / 58 (1.72%)
occurrences (all)	3	1	1
Urinary tract infection			
subjects affected / exposed	2 / 60 (3.33%)	1 / 57 (1.75%)	1 / 58 (1.72%)
occurrences (all)	2	1	1
Influenza			

subjects affected / exposed	2 / 60 (3.33%)	1 / 57 (1.75%)	3 / 58 (5.17%)
occurrences (all)	2	1	3
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	3 / 60 (5.00%)	2 / 57 (3.51%)	1 / 58 (1.72%)
occurrences (all)	3	2	1

Non-serious adverse events	K-877 0.2 mg twice daily	K-877 0.1 mg once daily	K-877 0.2 mg once daily
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 57 (52.63%)	22 / 58 (37.93%)	29 / 58 (50.00%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	4 / 58 (6.90%)
occurrences (all)	0	1	4
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 57 (7.02%)	2 / 58 (3.45%)	3 / 58 (5.17%)
occurrences (all)	4	2	3
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 57 (5.26%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	3	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	1 / 57 (1.75%)	4 / 58 (6.90%)	0 / 58 (0.00%)
occurrences (all)	1	4	0
Muscle spasms			
subjects affected / exposed	3 / 57 (5.26%)	0 / 58 (0.00%)	1 / 58 (1.72%)
occurrences (all)	3	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 57 (8.77%)	2 / 58 (3.45%)	4 / 58 (6.90%)
occurrences (all)	5	2	4
Urinary tract infection			

subjects affected / exposed	1 / 57 (1.75%)	2 / 58 (3.45%)	1 / 58 (1.72%)
occurrences (all)	1	2	1
Influenza			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	3 / 58 (5.17%)
occurrences (all)	0	1	3

Non-serious adverse events	K-877 0.4 mg once daily		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 59 (50.85%)		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4 4 / 59 (6.78%) 4 1 / 59 (1.69%) 1		
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2013	The protocol was amended to modify the followings. - Diaphragm with spermicide as an effective method of contraception for male or female study participants was removed from the inclusion criteria. - The inclusion criteria was added to require male study participants to use a condom with a spermicide during sexual intercourse, from screening to the end of the study, even if their sexual partner is or may be pregnant. - Subgroup analyses and non-compartmental PK analysis methods were added to the statistical analyses.
18 March 2014	The protocol was amended to allow for the inclusion of subjects who are taking the maximum tolerated dose of statin and still have not reached the LDL-C targets as defined in the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported