



Clinical trial results:

Dose response and safety of an oral PCSK9i, NNC0385-0434, in patients with established atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction

Summary

EudraCT number	2020-002630-32
Trial protocol	DE GR NL BE PL
Global end of trial date	20 June 2022

Results information

Result version number	v1 (current)
This version publication date	04 July 2023
First version publication date	04 July 2023

Trial information

Trial identification

Sponsor protocol code	NN6435-4697
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04992065
WHO universal trial number (UTN)	U1111-1252-3392

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority of three dose levels of oral NNC0385-0434 versus placebo on percent change in low-density lipoprotein cholesterol (LDL-C) from baseline to week 12 in subjects with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and International Council of Harmonisation (ICH) Good Clinical Practice, including archiving of essential documents and Food and Drug Administration (FDA) 21 Code of Federal Regulation (CFR) 312.120.

Background therapy:

Subjects were to continue their background medication (maximally tolerated dose of statins and other lipid-lowering therapies [except proprotein convertase subtilisin/kexin type 9 inhibition {PCSK9i} therapy, PCSK9 small interfering ribonucleic acid {siRNA} therapy and oral semaglutide therapy]) throughout the entire trial.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	03 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Greece: 31
Country: Number of subjects enrolled	Japan: 29
Country: Number of subjects enrolled	Netherlands: 47
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	United States: 57
Worldwide total number of subjects	267
EEA total number of subjects	181

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)	128
From 65 to 84 years	139
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 42 sites in 7 countries as follows (number of sites that screened subjects/ number of sites that randomised subjects): Belgium (5/ 5); Germany (4/ 4); Greece (6/ 6); Japan (4/ 4); Netherlands (6/ 6); Poland (5/ 5); United States (12/ 12).

Pre-assignment

Screening details:

Subjects were randomized to receive either one of 3 dose levels of NNC0385-0434, placebo (matched to NNC0385-0434) or evolocumab for 12 weeks.

Period 1

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

Blinding implementation details:

The trial was double-blinded within dose level of oral NNC0385-0434 and size matched placebo arm. The subcutaneous (s.c.) evolocumab arm was open label.

Arms

Are arms mutually exclusive?	Yes
Arm title	NNC0385-0434 15 mg

Arm description:

Subjects received 15 milligrams (mg) NNC0385-0434 (co-formulated with 500 mg salcaprozate sodium [SNAC]) tablet orally once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	NNC0385-0434 A 15 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 15 mg NNC0385-0434 once daily in the morning in a fasting state. Subjects were advised to take tablet at least 30 minutes (min) before the first food, beverage or other oral medications of the day with up to half a glass of water (approximately 120 milliliters [mL]/ 4 fluid ounces).

Arm title	NNC0385-0434 40 mg
------------------	--------------------

Arm description:

Subjects received 40 mg NNC0385-0434 (co-formulated with 500 mg SNAC) tablet orally once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	NNC0385-0434 A 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 40 mg NNC0385-0434 once daily in the morning in a fasting state. Subjects were advised to take tablet at least 30 min before the first food, beverage or other oral medications of the day with up to half a glass of water (approximately 120 mL/ 4 fluid ounces).

Arm title	NNC0385-0434 100 mg
------------------	---------------------

Arm description:

Subjects received 100 mg NNC0385-0434 (co-formulated with 500 mg SNAC) tablet orally once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	NNC0385-0434 A 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 100 mg NNC0385-0434 once daily in the morning in a fasting state. Subjects were advised to take tablet at least 30 min before the first food, beverage or other oral medications of the day with up to half a glass of water (approximately 120 mL/ 4 fluid ounces).

Arm title	Placebo
------------------	---------

Arm description:

Subjects received placebo matched to NNC0385-0434 (without SNAC) tablet orally once daily for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to NNC0385-0434)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to NNC0385-0434 once daily in the morning in a fasting state. Subjects were advised to take tablet at least 30 min before the first food, beverage or other oral medications of the day with up to half a glass of water (approximately 120 mL/ 4 fluid ounces).

Arm title	Evolocumab 140 mg
------------------	-------------------

Arm description:

Subjects received 140 mg evolocumab injection s.c. once every weeks for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Repatha®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 140 mg evolocumab injection once every 2 weeks into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated. The evolocumab was injected using a pre-filled SureClick® autoinjector (single-use).

Number of subjects in period 1	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg
Started	53	53	53
Completed	53	53	53

Number of subjects in period 1	Placebo	Evolocumab 140 mg
Started	54	54

Completed	54	54
-----------	----	----

Baseline characteristics

Reporting groups

Reporting group title	NNC0385-0434 15 mg
Reporting group description: Subjects received 15 milligrams (mg) NNC0385-0434 (co-formulated with 500 mg salcaprozate sodium [SNAC]) tablet orally once daily for 12 weeks.	
Reporting group title	NNC0385-0434 40 mg
Reporting group description: Subjects received 40 mg NNC0385-0434 (co-formulated with 500 mg SNAC) tablet orally once daily for 12 weeks.	
Reporting group title	NNC0385-0434 100 mg
Reporting group description: Subjects received 100 mg NNC0385-0434 (co-formulated with 500 mg SNAC) tablet orally once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description: Subjects received placebo matched to NNC0385-0434 (without SNAC) tablet orally once daily for 12 weeks.	
Reporting group title	Evolocumab 140 mg
Reporting group description: Subjects received 140 mg evolocumab injection s.c. once every weeks for 12 weeks.	

Reporting group values	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg
Number of subjects	53	53	53
Age Categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	64.1 ± 9.3	64.6 ± 8.6	65.2 ± 9.2
Gender Categorical Units: Subjects			
Female	17	17	14
Male	36	36	39

Reporting group values	Placebo	Evolocumab 140 mg	Total
Number of subjects	54	54	267
Age Categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	63.1 ± 8.6	64.5 ± 9.6	-
Gender Categorical Units: Subjects			
Female	17	17	82

Male	37	37	185
------	----	----	-----

End points

End points reporting groups

Reporting group title	NNC0385-0434 15 mg
Reporting group description: Subjects received 15 milligrams (mg) NNC0385-0434 (co-formulated with 500 mg salcaprozate sodium [SNAC]) tablet orally once daily for 12 weeks.	
Reporting group title	NNC0385-0434 40 mg
Reporting group description: Subjects received 40 mg NNC0385-0434 (co-formulated with 500 mg SNAC) tablet orally once daily for 12 weeks.	
Reporting group title	NNC0385-0434 100 mg
Reporting group description: Subjects received 100 mg NNC0385-0434 (co-formulated with 500 mg SNAC) tablet orally once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description: Subjects received placebo matched to NNC0385-0434 (without SNAC) tablet orally once daily for 12 weeks.	
Reporting group title	Evolocumab 140 mg
Reporting group description: Subjects received 140 mg evolocumab injection s.c. once every weeks for 12 weeks.	

Primary: Change in low-density lipoprotein (LDL)-cholesterol

End point title	Change in low-density lipoprotein (LDL)-cholesterol
End point description: Percentage change in LDL-cholesterol (LDL-C) (measured in milligrams per deciliter [mg/dL]) at week 12 is presented. Data is reported for the on-treatment period. The on-treatment period is the time period where subjects were considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following: The follow-up visit or the last date on randomised treatment regimen + 58 days or the end-date for the 'in-trial' observation period. The in-trial period is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. Full analysis set (FAS) included all randomized subjects. Number of subjects analyzed = subjects with available data for this endpoint.	
End point type	Primary
End point timeframe: From baseline (week 0) to visit 9 (week 12)	

End point values	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	52	49	52
Units: Percentage change of LDL-cholesterol				
arithmetic mean (standard deviation)	-27 (± 19)	-41 (± 37)	-55 (± 20)	6 (± 41)

End point values	Evolocumab 140 mg			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Percentage change of LDL-cholesterol				
arithmetic mean (standard deviation)	-59 (± 22)			

Statistical analyses

Statistical analysis title	NNC0385-0434 15 mg vs Placebo
Statistical analysis description:	
LDL-C percentage change at week 12 from baseline responses were analysed using an analysis of covariance model with randomised treatment and strata as factors and baseline LDL-C as covariate.	
Comparison groups	NNC0385-0434 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	-31.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.02
upper limit	-20.87

Statistical analysis title	NNC0385-0434 40 mg vs Placebo
Statistical analysis description:	
LDL-C percentage change at week 12 from baseline responses were analysed using an analysis of covariance model with randomised treatment and strata as factors and baseline LDL-C as covariate.	
Comparison groups	NNC0385-0434 40 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	-44.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.04
upper limit	-33.79

Statistical analysis title	NNC0385-0434 100 mg vs Evolocumab 140 mg
Statistical analysis description:	
LDL-C percentage change at week 12 from baseline responses were analysed using an analysis of covariance model with randomised treatment and strata as factors and baseline LDL-C as covariate.	
Comparison groups	NNC0385-0434 100 mg v Evolocumab 140 mg
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment Difference
Point estimate	3.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.81
upper limit	14.68

Statistical analysis title	NNC0385-0434 15 mg vs Evolocumab 140 mg
Statistical analysis description:	
LDL-C percentage change at week 12 from baseline responses were analysed using an analysis of covariance model with randomised treatment and strata as factors and baseline LDL-C as covariate.	
Comparison groups	NNC0385-0434 15 mg v Evolocumab 140 mg
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment Difference
Point estimate	33.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.16
upper limit	44.47

Statistical analysis title	NNC0385-0434 40 mg vs Evolocumab 140 mg
Statistical analysis description:	
LDL-C percentage change at week 12 from baseline responses were analysed using an analysis of covariance model with randomised treatment and strata as factors and baseline LDL-C as covariate.	
Comparison groups	NNC0385-0434 40 mg v Evolocumab 140 mg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment Difference
Point estimate	20.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.21
upper limit	31.48

Statistical analysis title	NNC0385-0434 100 mg vs Placebo
Statistical analysis description: LDL-C percentage change at week 12 from baseline responses were analysed using an analysis of covariance model with randomised treatment and strata as factors and baseline LDL-C as covariate.	
Comparison groups	NNC0385-0434 100 mg v Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	-61.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-72.94
upper limit	-50.72

Secondary: Change in total cholesterol

End point title	Change in total cholesterol
End point description: Percentage change in total cholesterol (measured in millimoles per liter [mmol/L]) at week 12 is presented. Data is reported for the on-treatment period. The on-treatment period is the time period where subjects were considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following: The follow-up visit or the last date on randomised treatment regimen + 58 days or the end-date for the 'in-trial' observation period. FAS included all randomized subjects. Number of subjects analyzed = subjects with available data for this endpoint.	
End point type	Secondary
End point timeframe: From baseline (week 0) to visit 9 (week 12)	

End point values	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	50	53
Units: Percentage change of total cholesterol				
arithmetic mean (standard deviation)	-14 (± 13)	-25 (± 27)	-33 (± 11)	4 (± 23)

End point values	Evolocumab 140 mg			
-------------------------	----------------------	--	--	--

Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Percentage change of total cholesterol				
arithmetic mean (standard deviation)	-38 (± 14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in high-density lipoprotein (HDL)-cholesterol

End point title	Change in high-density lipoprotein (HDL)-cholesterol
-----------------	--

End point description:

Percentage change in HDL-cholesterol (measured in mg/dL) at week 12 is presented. Data is reported for the on-treatment period. The on-treatment period is the time period where subjects were considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following: The follow-up visit or the last date on randomised treatment regimen + 58 days or the end-date for the 'in-trial' observation period. FAS included all randomized subjects. Number of subjects analyzed = subjects with available data for this endpoint.

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

End point timeframe:

From baseline (week 0) to visit 9 (week 12)

End point values	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	47	53
Units: Percentage change of HDL-cholesterol				
arithmetic mean (standard deviation)	4 (± 13)	5 (± 16)	7 (± 16)	1 (± 14)

End point values	Evolocumab 140 mg			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Percentage change of HDL-cholesterol				
arithmetic mean (standard deviation)	5 (± 14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in very low-density lipoprotein (VLDL)-cholesterol

End point title	Change in very low-density lipoprotein (VLDL)-cholesterol
End point description:	
Percentage change in VLDL-cholesterol (measured in mmol/L) at week 12 is presented. Data is reported for the on-treatment period. The on-treatment period is the time period where subjects were considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following: The follow-up visit or the last date on randomised treatment regimen + 58 days or the end-date for the 'in-trial' observation period. FAS included all randomized subjects. Overall number of subjects analyzed = subjects with available data for this endpoint.	
End point type	Secondary
End point timeframe:	
From baseline (week 0) to visit 9 (week 12)	

End point values	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	50	53
Units: Percentage change of VLDL cholesterol				
arithmetic mean (standard deviation)	5 (± 27)	-7 (± 33)	-15 (± 26)	3 (± 41)

End point values	Evolocumab 140 mg			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Percentage change of VLDL cholesterol				
arithmetic mean (standard deviation)	-16 (± 24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in triglycerides

End point title	Change in triglycerides
End point description:	
Percentage change in triglycerides (measured in mg/dL) at week 12 is presented. Data is reported for the on-treatment period. The on-treatment period is the time period where subjects were considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following: The follow-up visit or the last date on randomised treatment regimen + 58 days or the end-date for the 'in-trial' observation period. FAS included all randomized subjects. Overall number of subjects analyzed = subjects with available data for this endpoint.	
End point type	Secondary
End point timeframe:	
From baseline (week 0) to visit 9 (week 12)	

End point values	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	50	53
Units: Percentage change of triglycerides				
arithmetic mean (standard deviation)	5 (± 27)	-7 (± 31)	-16 (± 27)	2 (± 41)

End point values	Evolocumab 140 mg			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Percentage change of triglycerides				
arithmetic mean (standard deviation)	-16 (± 23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in total Apolipoprotein B (Apo B)

End point title	Change in total Apolipoprotein B (Apo B)
-----------------	--

End point description:

Percentage change in Apo B (measured in mg/dL) at week 12 is presented. Data is reported for the on-treatment period. The on-treatment period is the time period where subjects were considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following: The follow-up visit or the last date on randomised treatment regimen + 58 days or the end-date for the 'in-trial' observation period. FAS included all randomized subjects. Overall number of subjects analyzed = subjects with available data for this endpoint.

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

End point timeframe:

From baseline (week 0) to visit 9 (week 12)

End point values	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	52	49	53
Units: Percentage change of Apo B				
arithmetic mean (standard deviation)	-20 (± 15)	-34 (± 28)	-48 (± 12)	6 (± 31)

End point values	Evolocumab 140 mg			
Subject group type	Reporting group			
Number of subjects analysed	53			

Units: Percentage change of Apo B				
arithmetic mean (standard deviation)	-52 (± 17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in total Apolipoprotein CIII (Apo CIII)

End point title	Change in total Apolipoprotein CIII (Apo CIII)
-----------------	--

End point description:

Percentage change in Apo CIII (measured in mg/dL) at week 12 is presented. Data is reported for the on-treatment period. The on-treatment period is the time period where subjects were considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following: The follow-up visit or the last date on randomised treatment regimen + 58 days or the end-date for the 'in-trial' observation period. FAS included all randomized subjects. Overall number of subjects analyzed = subjects with available data for this endpoint.

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

End point timeframe:

From baseline (week 0) to visit 9 (week 12)

End point values	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	52	48	51
Units: Percentage change of Apo CIII				
arithmetic mean (standard deviation)	-0 (± 20)	-7 (± 24)	-16 (± 15)	2 (± 23)

End point values	Evolocumab 140 mg			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Percentage change of Apo CIII				
arithmetic mean (standard deviation)	-15 (± 21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in total lipoprotein(a) (Lp[a])

End point title	Change in total lipoprotein(a) (Lp[a])
-----------------	--

End point description:

Change in total Lp(a) (measured in mg/dL) at week 12 is presented as ratio to baseline. Data is

reported for the on-treatment period. The on-treatment period is the time period where subjects were considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following: The follow-up visit or the last date on randomised treatment regimen + 58 days or the end-date for the 'in-trial' observation period. FAS included all randomized subjects. Overall number of subjects analyzed = subjects with available data for this endpoint.

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

End point timeframe:

From baseline (week 0) to visit 9 (week 12)

End point values	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	50	53
Units: Ratio of Lipoprotein (a)				
geometric mean (geometric coefficient of variation)	0.79 (± 34.2)	0.70 (± 37.6)	0.66 (± 40.0)	0.99 (± 31.5)

End point values	Evolocumab 140 mg			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Ratio of Lipoprotein (a)				
geometric mean (geometric coefficient of variation)	0.59 (± 43.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-emergent adverse events (TEAEs)

End point title	Treatment-emergent adverse events (TEAEs)
-----------------	---

End point description:

An adverse events (AE) is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP. All presented AEs are TEAEs. TEAEs was the number of AEs recorded during the on-treatment period. The on-treatment period is the time period where subjects were considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following: The follow-up visit or the last date on randomised treatment regimen + 58 days or the end-date for the 'in-trial' observation period. Safety analysis set (SAS) included all subjects randomly assigned to trial treatment and who took at least 1 dose of trial product.

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

End point timeframe:

From baseline (week 0) to visit 10 (19 weeks + 4 days)

End point values	NNC0385-0434 15 mg	NNC0385-0434 40 mg	NNC0385-0434 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	53	54
Units: Events	82	60	65	56

End point values	Evolocumab 140 mg			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Events	81			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline (week 0) to visit 10 (19 weeks + 4 days)

Adverse event reporting additional description:

All presented AEs are TEAEs. TEAEs are AEs recorded during the on-treatment period. SAS included all subjects randomly assigned to trial treatment and who took at least 1 dose of trial product.

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

Dictionary used

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

Dictionary version	25
--------------------	----

Reporting groups

Reporting group title	NNC0385-0434 15 mg
-----------------------	--------------------

Reporting group description:

Subjects received 15 milligrams (mg) NNC0385-0434 (co-formulated with 500 mg salcaprozate sodium [SNAC]) tablet orally once daily for 12 weeks.

Reporting group title	NNC0385-0434 40 mg
-----------------------	--------------------

Reporting group description:

Subjects received 40 mg NNC0385-0434 (co-formulated with 500 mg SNAC) tablet orally once daily for 12 weeks.

Reporting group title	Evolocumab 140 mg
-----------------------	-------------------

Reporting group description:

Subjects received 140 mg evolocumab injection s.c. once every weeks for 12 weeks.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Subjects received placebo matched to NNC0385-0434 (without SNAC) tablet orally once daily for 12 weeks.

Reporting group title	NNC0385-0434 100 mg
-----------------------	---------------------

Reporting group description:

Subjects received 100 mg NNC0385-0434 (co-formulated with 500 mg SNAC) tablet orally once daily for 12 weeks.

Serious adverse events	NNC0385-0434 15 mg	NNC0385-0434 40 mg	Evolocumab 140 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 53 (1.89%)	3 / 53 (5.66%)	3 / 54 (5.56%)
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)			
Oesophageal adenocarcinoma			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (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
Vascular disorders			

Peripheral artery aneurysm			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 54 (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
Cardiac disorders			
Diastolic dysfunction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelopathy			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (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
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 54 (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
Non-cardiac chest pain			

subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 54 (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
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (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
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (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			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (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
Pain in extremity			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (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			
Herpes zoster			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (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	Placebo	NNC0385-0434 100 mg	
Total subjects affected by serious			

adverse events			
subjects affected / exposed	5 / 54 (9.26%)	1 / 53 (1.89%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral artery aneurysm			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Diastolic dysfunction			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			

subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NNC0385-0434 15 mg	NNC0385-0434 40 mg	Evolocumab 140 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 53 (30.19%)	14 / 53 (26.42%)	17 / 54 (31.48%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	5 / 54 (9.26%)
occurrences (all)	0	1	5
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 53 (7.55%)	0 / 53 (0.00%)	3 / 54 (5.56%)
occurrences (all)	4	0	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 53 (7.55%)	4 / 53 (7.55%)	1 / 54 (1.85%)
occurrences (all)	4	4	1
Constipation			
subjects affected / exposed	3 / 53 (5.66%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences (all)	3	0	0
Nausea			
subjects affected / exposed	1 / 53 (1.89%)	3 / 53 (5.66%)	0 / 54 (0.00%)
occurrences (all)	1	4	0

Dyspepsia subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 2	0 / 53 (0.00%) 0	1 / 54 (1.85%) 1
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 53 (0.00%) 0	3 / 54 (5.56%) 3
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 4	0 / 53 (0.00%) 0	2 / 54 (3.70%) 2
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 3 1 / 53 (1.89%) 1	8 / 53 (15.09%) 8 3 / 53 (5.66%) 4	6 / 54 (11.11%) 6 0 / 54 (0.00%) 0

Non-serious adverse events	Placebo	NNC0385-0434 100 mg	
Total subjects affected by non-serious adverse events subjects affected / exposed	14 / 54 (25.93%)	19 / 53 (35.85%)	
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 4	3 / 53 (5.66%) 3	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2	0 / 53 (0.00%) 0	
Gastrointestinal disorders Diarrhoea			

subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	2 / 53 (3.77%) 5	
Constipation subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	3 / 53 (5.66%) 3	
Dyspepsia subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	3 / 53 (5.66%) 4	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0	
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2	0 / 53 (0.00%) 0	
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	6 / 54 (11.11%) 6	8 / 53 (15.09%) 8	
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3	2 / 53 (3.77%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported