



## Clinical trial results:

**A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, 12-Week Study of Pitavastatin in High-Risk Hyperlipidaemia in Childhood P/0230/2012, P/0231/2012, P/0232/2012 and P/0233/2012.**

### Summary

EudraCT number	2011-004964-32
Trial protocol	NL GR FR ES NO IT
Global end of trial date	20 March 2013

### Results information

Result version number	v1 (current)
This version publication date	01 February 2016
First version publication date	31 July 2015

### Trial information

#### Trial identification

Sponsor protocol code	NK-104-4.01EU
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#### 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 Co, Ltd., +44 (0)118 922 9000,
Scientific contact	Regulatory Affairs, Kowa Research Europe Co, Ltd., +44 (0)118 922 9000,

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000300-PIP01-08, EMA-000054-PIP01-07, EMA-000302-PIP01-08, EMA-000301-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	20 May 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 March 2013
Global end of trial reached?	Yes
Global end of trial date	20 March 2013
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of this study was to compare the efficacy of pitavastatin 1 mg QD, 2 mg QD, and 4 mg QD to placebo in terms of the percentage reduction in LDL-C in children or adolescent patients with high-risk hyperlipidaemia at steady state (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.

Patients were discouraged from starting any new medication without first consulting the Investigator, unless the new medication was required for emergency use. In general, any medication not excluded by the protocol was permitted.

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Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Netherlands: 40
Country: Number of subjects enrolled	Norway: 15
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Greece: 22
Country: Number of subjects enrolled	Italy: 15
Worldwide total number of subjects	106
EEA total number of subjects	106

Notes:

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**Subjects enrolled per age group**

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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)	67
Adolescents (12-17 years)	39
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study consisted of an up to 5-week screening/wash out period, and all participants were screened at specialist lipid clinics.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Pitavastatin 1 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Pitavastatin
Investigational medicinal product code	NK-104
Other name	PITAVASTATIN CALCIUM
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pitavastatin 1 mg was to be taken orally, once daily in the morning. Duration of treatment is 12 weeks.

<b>Arm title</b>	Pitavastatin 2 mg
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Pitavastatin
Investigational medicinal product code	NK-104
Other name	PITAVASTATIN CALCIUM
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pitavastatin 2 mg was to be taken orally, once daily in the morning. Duration of treatment is 12 weeks.

<b>Arm title</b>	Pitavastatin 4 mg
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Pitavastatin
Investigational medicinal product code	NK-104
Other name	PITAVASTATIN CALCIUM
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pitavastatin was to be taken orally, once daily in the morning. Pitavastatin 2 mg was received for the first 4 weeks and then pitavastatin 4 mg for the remaining 8 weeks of the treatment period.

<b>Arm title</b>	Placebo group
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Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was to be taken orally, once daily in the morning. Duration of treatment is 12 weeks.

<b>Number of subjects in period 1</b>	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg
Started	26	27	26
Completed	26	26	24
Not completed	0	1	2
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	1	1

<b>Number of subjects in period 1</b>	Placebo group
Started	27
Completed	27
Not completed	0
Consent withdrawn by subject	-
Adverse event, non-fatal	-

## Baseline characteristics

### Reporting groups

Reporting group title	Pitavastatin 1 mg
Reporting group description: -	
Reporting group title	Pitavastatin 2 mg
Reporting group description: -	
Reporting group title	Pitavastatin 4 mg
Reporting group description: -	
Reporting group title	Placebo group
Reporting group description: -	

Reporting group values	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg
Number of subjects	26	27	26
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	15	15	17
Adolescents (12-17 years)	11	12	9
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	10.5	11.1	10.3
standard deviation	± 2.75	± 2.87	± 2.66
Gender categorical			
Units: Subjects			
Female	14	17	12
Male	12	10	14

Reporting group values	Placebo group	Total	
Number of subjects	27	106	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	20	67	
Adolescents (12-17 years)	7	39	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	

85 years and over	0	0	
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Age continuous			
Units: years			
arithmetic mean	10.4		
standard deviation	± 3.26	-	
Gender categorical			
Units: Subjects			
Female	15	58	
Male	12	48	

## End points

### End points reporting groups

Reporting group title	Pitavastatin 1 mg
Reporting group description: -	
Reporting group title	Pitavastatin 2 mg
Reporting group description: -	
Reporting group title	Pitavastatin 4 mg
Reporting group description: -	
Reporting group title	Placebo group
Reporting group description: -	
Subject analysis set title	Pitavastatin 1 mg vs. Placebo
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set was defined as all randomized patients who received at least 1 dose of study drug and had a valid baseline lipid measurement and at least 1 valid post-baseline lipid measurement.	
Subject analysis set title	Pitavastatin 2 mg vs. Placebo
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set was defined as all randomized patients who received at least 1 dose of study drug and had a valid baseline lipid measurement and at least 1 valid post-baseline lipid measurement.	
Subject analysis set title	Pitavastatin 4 mg vs. Placebo
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set was defined as all randomized patients who received at least 1 dose of study drug and had a valid baseline lipid measurement and at least 1 valid post-baseline lipid measurement.	

### Primary: The primary efficacy endpoint of this study was the percent change in LDL-C from baseline to Week 12 with LOCF

End point title	The primary efficacy endpoint of this study was the percent change in LDL-C from baseline to Week 12 with LOCF
End point description:	
End point type	Primary
End point timeframe: From baseline to Week 12	

End point values	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg	Placebo group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	24	27
Units: percent change in LDL-C				
least squares mean (standard error)	-23.5 (± 2.09)	-30.1 (± 2.11)	-39.3 (± 2.18)	1 (± 2.06)

## Statistical analyses



<b>Statistical analysis title</b>	Pitavastatin 1 mg vs. Placebo
Comparison groups	Pitavastatin 1 mg v Placebo group
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-24.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.3
upper limit	-18.6
Variability estimate	Standard error of the mean
Dispersion value	2.94

<b>Statistical analysis title</b>	Pitavastatin 2 mg vs. Placebo
Comparison groups	Pitavastatin 2 mg v Placebo group
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-31.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37
upper limit	-25.2
Variability estimate	Standard error of the mean
Dispersion value	2.96

<b>Statistical analysis title</b>	Pitavastatin 4 mg vs. Placebo
Comparison groups	Pitavastatin 4 mg v Placebo group
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-40.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.2
upper limit	-34.4
Variability estimate	Standard error of the mean
Dispersion value	2.99

### Secondary: Percent change in LDL-C from baseline over 12 weeks of treatment

End point title	Percent change in LDL-C from baseline over 12 weeks of treatment
End point description:	
End point type	Secondary
End point timeframe:	
From baseline over 12 weeks of treatment (Week 4, Week 8, and Week 12)	

End point values	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg	Placebo group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	24	27
Units: Percent change in LDL-C				
number (not applicable)				
Percent change in week 4	-24.1	-31.1	-28.7	0.5
Percent change in week 8	-24.2	-20.7	-39.5	-1.5
Percent change in week 12	-23.3	-29.7	-40.3	1.3

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentages of patients who achieved American Heart Association minimal (130 mg/dL [3.4 mmol/L]) and ideal (110 mg/dL [2.8 mmol/L]) LDL-C targets

End point title	Percentages of patients who achieved American Heart Association minimal (130 mg/dL [3.4 mmol/L]) and ideal (110 mg/dL [2.8 mmol/L]) LDL-C targets
End point description:	
End point type	Secondary
End point timeframe:	
From baseline to week 12 with LOCF	

End point values	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg	Placebo group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	24	27
Units: Percentages of patients				
number (not applicable)				
LDL-C <130 mg/dL	3.8	30.8	37.5	0
LDL-C <110 mg/dL	0	7.7	16.7	0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent changes in HDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), TG, apolipoprotein A1 (Apo A1), and apolipoprotein B (Apo B)

End point title	Percent changes in HDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), TG, apolipoprotein A1 (Apo A1), and apolipoprotein B (Apo B)
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End point description:

End point type	Secondary
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End point timeframe:

From baseline to week 12 with LOCF

End point values	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg	Placebo group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	24	27
Units: Percent change				
least squares mean (standard error)				
HDL-C	6.1 (± 2.5)	-2.4 (± 2.52)	-3.1 (± 2.61)	1.1 (± 2.46)
non-HDL	-22.9 (± 2.14)	-28.5 (± 2.15)	-37.2 (± 2.23)	1.1 (± 2.1)
TC	-17.8 (± 1.78)	-24.2 (± 1.79)	-31.3 (± 1.86)	0.9 (± 1.75)
TG	-7.6 (± 6.26)	-5.9 (± 6.43)	0.3 (± 6.6)	2 (± 6.15)
Apo A1	1.1 (± 2.16)	-3.6 (± 2.16)	-2.2 (± 2.24)	-0.8 (± 2.12)
Apo B	-21.6 (± 2.24)	-25 (± 2.25)	-28.8 (± 2.33)	0.4 (± 2.2)

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Changes in TC:HDL-C ratio, non-HDL-C:HDL-C ratio, and Apo B:Apo A1 ratio**

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End point title	Changes in TC:HDL-C ratio, non-HDL-C:HDL-C ratio, and Apo B:Apo A1 ratio
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End point description:

End point type	Secondary
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End point timeframe:

From baseline to week 12 with LOCF

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End point values	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg	Placebo group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	24	27
Units: Ratio				
least squares mean (standard error)				
TC:HDL-C ratio	-1.36 (± 0.151)	-1.32 (± 0.152)	-1.73 (± 0.157)	-0.04 (± 0.148)
non-HDL-C:HDL-C ratio	-1.36 (± 0.151)	-1.32 (± 0.152)	-1.73 (± 0.157)	-0.04 (± 0.148)
Apo B:Apo A1 ratio	-0.25 (± 0.032)	-0.24 (± 0.032)	-0.3 (± 0.033)	0 (± 0.031)

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The evaluation of safety during the double-blind period was based primarily on the frequency of adverse events, SAEs, discontinuations due to adverse events, clinical laboratory assessments etc.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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### Reporting groups

Reporting group title	Pitavastatin 1 mg
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Reporting group description: -	
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Reporting group title	Pitavastatin 2 mg
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Reporting group description: -	
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Reporting group title	Pitavastatin 4 mg
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Reporting group description: -	
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Reporting group title	Placebo
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Reporting group description: -	
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Serious adverse events	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	0 / 26 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Facial bones fracture			

subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

<b>Non-serious adverse events</b>	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 26 (69.23%)	16 / 27 (59.26%)	11 / 26 (42.31%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 26 (23.08%)	5 / 27 (18.52%)	1 / 26 (3.85%)
occurrences (all)	7	7	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 26 (11.54%)	2 / 27 (7.41%)	0 / 26 (0.00%)
occurrences (all)	3	3	0
Abdominal discomfort			
subjects affected / exposed	1 / 26 (3.85%)	0 / 27 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 26 (15.38%)	6 / 27 (22.22%)	2 / 26 (7.69%)
occurrences (all)	4	6	2
Influenza			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 26 (7.69%)	0 / 27 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0

<b>Non-serious adverse events</b>	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 27 (55.56%)		

Nervous system disorders			
Headache			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Abdominal discomfort			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	6		
Influenza			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported