Clinical trial results:
A 52-Week Open-Label Extension and Safety 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	2011-004983-32
Trial protocol	GR NL FR ES NO IT
Global end of trial date	10 June 2014

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-104-4.02EU

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 (0)118 922 9000,
Scientific contact	Regulatory Affairs, Kowa Research Europe, 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)	EMEA-000300-PIP01-08, EMEA-000054-PIP01-07, EMEA-000302-PIP01-08, EMEA-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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2014
Global end of trial reached?	Yes
Global end of trial date	10 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the safety of pitavastatin 1 mg QD, 2 mg QD, and 4 mg QD in children or adolescent patients with high-risk hyperlipidaemia over a period of 52 weeks.

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, both prescribed and over-the-counter, without consulting the Investigator unless the new medication was required for emergency use. In general, any medication not excluded by the protocol was permitted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2012
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	Netherlands: 48
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Greece: 23
Country: Number of subjects enrolled	Italy: 26
Worldwide total number of subjects	113
EEA total number of subjects	113

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)	67

Adolescents (12-17 years)	46
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study included patients who completed the 12-week, double-blind study NK-104-4.01EU (EudraCT 2011-004964-32), but was also open for enrollment by eligible children and adolescents who were not enrolled in the double-blind study.

Pre-assignment

Screening details:

For patients who were not enrolled in the double-blind study, a 5 weeks screening/washout period occurred before the start of dosing. No screening/washout period was required for patients who entered this study upon completion of the double-blind study.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Pitavastatin 1, 2 or 4 mg

Arm description:

All patients started from 1 mg and were up-titrated to 2 or 4 mg in step-wise manner in an effort to achieve a LDL-C treatment target (<110 mg/dL) so long as the dose was tolerated.

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 tablet 1, 2 or 4 mg were to be taken orally, once daily in the morning. Duration of treatment was 52 weeks.

Number of subjects in period 1[1]	Pitavastatin 1, 2 or 4 mg
Started	112
Completed	99
Not completed	13
Fasting LDL-C >130 mg/dL (3.4 mmol/L)	1
Consent withdrawn by subject	10
Adverse event, non-fatal	1
-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One Patient was enrolled into the study, but withdrew consent before receiving any study drug. The patient was therefore not included in any specific dose level, but was included in the patient

total.

Baseline characteristics

Reporting groups	
Reporting group title	Pitavastatin 1, 2 or 4 mg

Reporting group description:

All patients started from 1 mg and were up-titrated to 2 or 4 mg in step-wise manner in an effort to achieve a LDL-C treatment target (<110 mg/dL) so long as the dose was tolerated.

Reporting group values	Pitavastatin 1, 2 or 4 mg	Total	
Number of subjects	112	112	
Age categorical Units: Subjects			
Children (2-11 years)	67	67	
Adolescents (12-17 years)	45	45	
Age continuous Units: years			
arithmetic mean	10.8		
standard deviation	± 2.96	-	
Gender categorical Units: Subjects			
Female	58	58	
Male	54	54	

End points

End points reporting groups

Reporting group title	Pitavastatin 1, 2 or 4 mg

Reporting group description:

All patients started from 1 mg and were up-titrated to 2 or 4 mg in step-wise manner in an effort to achieve a LDL-C treatment target (<110 mg/dL) so long as the dose was tolerated.

Primary: Percent change in LDL-C

End point title	Percent change in LDL-C[1]

End point description:

End point type	Primary

End point timeframe:

From baseline to week 52 with LOCF.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was an open-label safety study without any comparators; therefore, no formal statistical analysis for efficacy end points were executed.

End point values	Pitavastatin 1, 2 or 4 mg			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: Percent change in LDL-C				
arithmetic mean (standard deviation)	-37.8 (± 12.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of patients who achieved AHA 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 AHA 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 over 52 weeks of treatment.

End point values	Pitavastatin 1, 2 or 4 mg			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: Percentages of patients				
number (not applicable)				
LDL-C <130 mg/dL	42			
LDL-C <110 mg/dL	20.5			

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)

End point description:

End point type	Secondary

End point timeframe:

From baseline to week 52 with LOCF.

End point values	Pitavastatin 1, 2 or 4 mg			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: Percent change				
arithmetic mean (standard deviation)				
HDL-C	1.8 (± 16.29)			
non-HDL-C	-36 (± 12.03)			
TC	-29.5 (± 10.42)			
TG	-7.6 (± 32.08)			
Apo A1	-0.1 (± 13.93)			
Apo B	-32.4 (± 11.33)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

From baseline to week 52 with LOCF.

End point values	Pitavastatin 1, 2 or 4 mg			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: Ratio				
arithmetic mean (standard deviation)				
TC:HDL-C ratio	-1.87 (± 1.22)			
non-HDL-C:HDL-C ratio	-1.87 (± 1.22)			
Apo B:Apo A1 ratio	-0.36 (± 0.217)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting began from the time of informed consent/assent and ended at the conclusion of the study unless an unresolved adverse event was still being followed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Pitavastatin 1, 2 or 4 mg

Reporting group description:

All patients started from 1 mg and were up-titrated to 2 or 4 mg in step-wise manner in an effort to achieve a LDL-C treatment target (<110 mg/dL) so long as the dose was tolerated.

Serious adverse events	Pitavastatin 1, 2 or 4 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 112 (0.89%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Tonsillar inflammation			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pitavastatin 1, 2 or 4 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 112 (66.96%)		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 112 (8.04%)		
occurrences (all)	18		
General disorders and administration site conditions			

Influenza like illness subjects affected / exposed occurrences (all)	9 / 112 (8.04%) 10		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 7		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 112 (2.68%) 3 3 / 112 (2.68%) 3		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	3 / 112 (2.68%) 3 3 / 112 (2.68%) 4		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Gastroenteritis viral subjects affected / exposed occurrences (all) Tonsillitis subjects affected / exposed occurrences (all) Upper respiratory tract infection	18 / 112 (16.07%) 22 12 / 112 (10.71%) 12 11 / 112 (9.82%) 15 4 / 112 (3.57%) 4		

subjects affected / exposed occurrences (all)	3 / 112 (2.68%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2012	Amendment 2 (Protocol v3.0) was written to modify the language about removing patients from the study due to failure to achieve the target LDL-C level of <130 mg/dL (3.4 mmol/L). Due to the lack of approved statin treatments available to paediatric patients at the time the study began, the study Investigators requested that they have discretion to maintain children in the trial if it was felt that there was no better therapy available outside the confines of the trial, rather than being required to withdraw them based solely on the LDL-C levels achieved. After the Investigator Meeting, this proposed modification to the study was presented to and supported by the independent DMC for this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported