

**Clinical trial results:****The Efficacy and Safety of ROSUvastatin Dose Titration in the Treatment of PATients with Hyperlipidemia (ROSU-PATH)****Summary**

EudraCT number	2012-004799-21
Trial protocol	SI CZ HU
Global end of trial date	31 July 2015

**Results information**

Result version number	v1 (current)
This version publication date	24 June 2020
First version publication date	24 June 2020
Summary attachment (see zip file)	ROSU-PATH Final Report Synopsis (Final report_KCT_03_ROSU-PATH-2016-03-FINAL-SYNOPSIS.docx)

**Trial information****Trial identification**

Sponsor protocol code	KCT03/2012
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**Additional study identifiers**

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

Notes:

**Sponsors**

Sponsor organisation name	Krka, d.d., Novo mesto
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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	29 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2015
Global end of trial reached?	Yes
Global end of trial date	31 July 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The aim of the study is to establish the efficacy and safety of Roswera® in wide populations of patients with primary hypercholesterolemia and mixed dyslipidemia (type IIb) (patients with high absolute risk for cardiovascular diseases in primary and secondary prevention) with emphasis on placement of additional strengths 15 mg and 30 mg in clinical practice.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that are based on the Declaration of Helsinki.

In general patients aged 18-75 years of both genders with primary hypercholesterolemia or mixed dyslipidemia (type IIb) were eligible for the inclusion in the study. Prior to any study activities patients needed to sign written informed consent form. The dose of Rosuvastatin was adjusted on V2 (4 weeks) and on V3 (8 weeks) according to trial scheme and target lipid values.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2013
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Long term follow-up planned	No
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Independent data monitoring committee (IDMC) involvement?	No
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Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Croatia: 50
Country: Number of subjects enrolled	Ukraine: 52
Country: Number of subjects enrolled	Russian Federation: 122
Country: Number of subjects enrolled	Romania: 54
Country: Number of subjects enrolled	Slovenia: 67
Country: Number of subjects enrolled	Czech Republic: 65
Country: Number of subjects enrolled	Hungary: 62
Worldwide total number of subjects	472
EEA total number of subjects	298

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)	367
From 65 to 84 years	105
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

There were 472 patients enrolled in the study.

### Pre-assignment

Screening details:

In general patients aged 18-75 years of both genders with primary hypercholesterolemia or mixed dyslipidemia (type IIb) were eligible for the inclusion in the study. Prior to any study activities patients needed to sign written informed consent form.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Group 10

Arm description:

All patients meeting inclusion criteria were randomized at the start of the trial course (Visit 1) into two groups to receive either 10 mg/day or 15 mg/day of rosuvastatin. On V2 (after 4 weeks) and V3 (after 8 weeks) the dose was adjusted according to achievement of target LDL-c goals. If the patient did not achieve target LDL-c goal, the dose was increased according to the trial scheme.

Patients starting the treatment with 10 mg/day of Roswera® were titrated according to the regimen 10 mg – 20 mg – 40 mg.

Patients starting the treatment with 15 mg/day of Roswera® were titrated according to the regimen 15 mg – 30 mg – 40 mg.

Arm type	Active comparator
Investigational medicinal product name	Roswera® 10
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet per day at any time during the day, throughout the trial at the same time. Roswera® 10 contains 10 mg of rosuvastatin per tablet.

Investigational medicinal product name	Roswera® 20
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet per day at any time during the day, throughout the trial at the same time. Roswera® 20 contains 20 mg of rosuvastatin per tablet.

Investigational medicinal product name	Roswera® 40
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet per day at any time during the day, throughout the trial at the same time. Roswera® 40 contains 40 mg of rosuvastatin per tablet.

<b>Arm title</b>	Group 15
Arm description: All patients meeting inclusion criteria were randomized at the start of the trial course (Visit 1) into two groups to receive either 10 mg/day or 15 mg/day of rosuvastatin. On V2 (after 4 weeks) and V3 (after 8 weeks) the dose was adjusted according to achievement of target LDL-c goals. If the patient did not achieve target LDL-c goal, the dose was increased according to the trial scheme. Patients starting the treatment with 10 mg/day of Roswera® were titrated according to the regimen 10 mg – 20 mg – 40 mg. Patients starting the treatment with 15 mg/day of Roswera® were titrated according to the regimen 15 mg – 30 mg – 40 mg.	
Arm type	Experimental
Investigational medicinal product name	Roswera® 15
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

**Dosage and administration details:**

1 tablet per day at any time during the day, throughout the trial at the same time. Roswera® 15 contains 15 mg of rosuvastatin per tablet.

Investigational medicinal product name	Roswera® 30
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

**Dosage and administration details:**

1 tablet per day at any time during the day, throughout the trial at the same time. Roswera® 30 contains 30 mg of rosuvastatin per tablet.

Investigational medicinal product name	Roswera® 40
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

**Dosage and administration details:**

1 tablet per day at any time during the day, throughout the trial at the same time. Roswera® 40 contains 40 mg of rosuvastatin per tablet.

<b>Number of subjects in period 1</b>	Group 10	Group 15
Started	239	233
Completed	215	212
Not completed	24	21
Physician decision	1	1
Consent withdrawn by subject	6	3
Adverse event, non-fatal	13	15
Lost to follow-up	1	-
Protocol deviation	3	2



## Baseline characteristics

### Reporting groups

Reporting group title

Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	472	472	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	56.9		
standard deviation	± 9.81	-	
Gender categorical			
Units: Subjects			
Female	225	225	
Male	246	246	
NA	1	1	

## End points

### End points reporting groups

Reporting group title	Group 10
Reporting group description: All patients meeting inclusion criteria were randomized at the start of the trial course (Visit 1) into two groups to receive either 10 mg/day or 15 mg/day of rosuvastatin. On V2 (after 4 weeks) and V3 (after 8 weeks) the dose was adjusted according to achievement of target LDL-c goals. If the patient did not achieve target LDL-c goal, the dose was increased according to the trial scheme. Patients starting the treatment with 10 mg/day of Roswera® were titrated according to the regimen 10 mg – 20 mg – 40 mg. Patients starting the treatment with 15 mg/day of Roswera® were titrated according to the regimen 15 mg – 30 mg – 40 mg.	
Reporting group title	Group 15
Reporting group description: All patients meeting inclusion criteria were randomized at the start of the trial course (Visit 1) into two groups to receive either 10 mg/day or 15 mg/day of rosuvastatin. On V2 (after 4 weeks) and V3 (after 8 weeks) the dose was adjusted according to achievement of target LDL-c goals. If the patient did not achieve target LDL-c goal, the dose was increased according to the trial scheme. Patients starting the treatment with 10 mg/day of Roswera® were titrated according to the regimen 10 mg – 20 mg – 40 mg. Patients starting the treatment with 15 mg/day of Roswera® were titrated according to the regimen 15 mg – 30 mg – 40 mg.	

### Primary: Efficacy of Roswera® in achieving target LDL-c levels

End point title	Efficacy of Roswera® in achieving target LDL-c levels
End point description: The primary efficacy endpoint was to evaluate efficacy of Roswera® in achieving 2011 ESC/EAS guidelines target LDL-c levels in patients with hyperlipidemia. At each control visit, the serum lipids were measured and according to results, the achievement of target lipid levels was obtained. During the trial, the proportion of patients achieving target LDL-c values was steadily increasing. At the end of the trial, 62% of patients in Group 10 and 73% of patients in Group 15 achieved target LDL-c levels.	
End point type	Primary
End point timeframe: 12 weeks for one patient and was the same for the whole duration of the study (FPI 14.3.2013 - LPO 31.7.2015).	

End point values	Group 10	Group 15		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	228		
Units: % of patients reaching target LDL-c				
number (not applicable)				
Visit 2 (4 weeks)	50	59		
Visit 3 (8 weeks)	59	74		
Visit 4 (12 weeks)	62	73		



## Statistical analyses

<b>Statistical analysis title</b>	Difference between groups
Statistical analysis description: Because of the reasonably large sample, the asymptotic z-test was employed to assess the difference between means of two variables measured in the same population. Asymptotic 95%-confidence interval for the difference between means was used for interval estimation. The difference in proportion of patients achieving target LDL-c levels was statistically significant between Group 10 and Group 15 on each control visit ( $p < 0.0001$ on V3 and V4; $p < 0.05$ on V2) and was in favour of Group 15.	
Comparison groups	Group 10 v Group 15
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	other
P-value	$< 0.05$
Method	asymptotic z-test

## Primary: LDL-c values across visits

End point title	LDL-c values across visits
End point description: The primary efficacy endpoint was to evaluate efficacy of Roswera® in achieving 2011 ESC/EAS guidelines target LDL-c levels in patients with hyperlipidemia. At each control visit, the serum lipids were measured and according to results, the achievement of target lipid levels was obtained. Group 10: The mean LDL-c values at the beginning and at the end of the trial were $4.33 \pm 1.11$ mmol/l and $2.36 \pm 0.72$ mmol/l, respectively. The mean LDL-c decreased statistically significantly from the V1 to V2 ( $p < 0.0001$ ) and from V2 to V3 ( $p < 0.0001$ ). Group 15: The mean LDL-c values at the beginning and at the end of the trial were $4.44 \pm 1.02$ mmol/l and $2.28 \pm 0.66$ mmol/l, respectively. The mean LDL-c decreased statistically significantly from the V1 to V2 ( $p < 0.0001$ ) and from V2 to V3 ( $p < 0.0001$ ).	
End point type	Primary
End point timeframe: 12 weeks for one patient and was the same for the whole duration of the study ( FPI 14.3.2013 - LPO 31.7.2015).	

End point values	Group 10	Group 15		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	232		
Units: mmol/l				
arithmetic mean (standard deviation)				
Visit 1 (baseline)	4.33 ( $\pm 1.11$ )	4.44 ( $\pm 1.02$ )		
Visit 2 (4 weeks)	2.64 ( $\pm 0.93$ )	2.52 ( $\pm 0.80$ )		
Visit 3 (8 weeks)	2.38 ( $\pm 0.76$ )	2.28 ( $\pm 0.71$ )		
Visit 4 (12 weeks)	2.36 ( $\pm 0.72$ )	2.28 ( $\pm 0.66$ )		

## Statistical analyses

<b>Statistical analysis title</b>	comparison between two visits
Statistical analysis description: Because of the reasonably large sample, the asymptotic z-test was employed to assess the difference between means of two variables measured in the same population. Asymptotic 95%-confidence interval for the difference between means was used for interval estimation.	
Comparison groups	Group 10 v Group 15
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Asymptotic z-test

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

12 weeks for one patient and was the same for the whole duration of the study (FPI 14.3.2013 - LPO 31.7.2015).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	All patients
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Reporting group description:

All 472 patients that were included in the ITT analysis.

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 472 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 472 (19.28%)		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 472 (2.33%)		
occurrences (all)	13		
Blood and lymphatic system disorders			
Blood creatine phosphokinase increased			
subjects affected / exposed	9 / 472 (1.91%)		
occurrences (all)	9		
General disorders and administration site conditions			
Insomnia			

subjects affected / exposed	5 / 472 (1.06%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	16 / 472 (3.39%)		
occurrences (all)	17		
Nausea			
subjects affected / exposed	12 / 472 (2.54%)		
occurrences (all)	12		
Diarrhoea			
subjects affected / exposed	10 / 472 (2.12%)		
occurrences (all)	12		
Flatulence			
subjects affected / exposed	10 / 472 (2.12%)		
occurrences (all)	13		
Constipation			
subjects affected / exposed	7 / 472 (1.48%)		
occurrences (all)	10		
Dyspepsia			
subjects affected / exposed	6 / 472 (1.27%)		
occurrences (all)	7		
Hepatobiliary disorders			
Hepatic enzyme increased			
subjects affected / exposed	6 / 472 (1.27%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	14 / 472 (2.97%)		
occurrences (all)	16		
Muscular weakness			
subjects affected / exposed	7 / 472 (1.48%)		
occurrences (all)	7		
Muscle spasms			
subjects affected / exposed	6 / 472 (1.27%)		
occurrences (all)	7		



## **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