Clinical trial results:
Modeling of the impact of a PCSK9 inhibition on lipoproteins in patients with dyslipidemia

Summary

EudraCT number	2016-003551-30
Trial protocol	DE
Global end of trial date	16 January 2019

Results information

Result version number	v2 (current)
This version publication date	18 February 2021
First version publication date	16 September 2020
Version creation reason	• Correction of full data set Correction of the primary completition data

Trial information

Trial identification

Sponsor protocol code	August2016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1192-0601
Other trial identifiers	DRKS: DRKS00011663

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Freiburg Institut für klinische Chemie und Laboratoriumsmedizin
Sponsor organisation address	Hugstetter Str 55, Freiburg, Germany, 79106
Public contact	Karl Winkler, Universitätsklinikum Freiburg Institut für klinische Chemie und Laboratoriumsmedizin , 49 76127033160, karl.winkler@uniklinik-freiburg.de
Scientific contact	Karl Winkler, Universitätsklinikum Freiburg Institut für klinische Chemie und Laboratoriumsmedizin , 49 76127033160, karl.winkler@uniklinik-freiburg.de

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	16 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 January 2019
Global end of trial reached?	Yes
Global end of trial date	16 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective is to study the impact of PCSK9 inhibitors in patients with dyslipidemia using a mathematical model describing the lipoproteins of low density (LDL)based on clinical data

Protection of trial subjects:

Study was part of regular patient treatment. Hence Protection=regular protection in patient treatment

Background therapy:

the protocol doesn't prescripe a background therapy

Evidence for comparator: -

Actual start date of recruitment	01 March 2017
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	Germany: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	16
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Time-span of recruitment: 23.03.17 -01.12.18
All patients were recruited in the lipid ambulance of the university hospital Freiburg, Germany

Pre-assignment

Screening details:

no screening, patients of the lipid ambulance of the university hospital Freiburg, Germany, who fulfilled the inclusion criteria were included (given written consent)

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Praluent arm

Arm description:

no PCSK9-inhibitor at baseline, start of PCSK9 inhibition thearpy directly after baseline-visit. visite 1 (~2 weeks after baseline-visit), visit 2 (~12 weeks after baseline visit)

Arm type	Experimental
Investigational medicinal product name	Praluent
Investigational medicinal product code	EMA/504805/2015
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

75 mg every two weeks

Arm title	Repatha arm

Arm description:

12 weeks Repatha

Arm type	Experimental
Investigational medicinal product name	Repatha
Investigational medicinal product code	EMEA/H/C/003766
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

140mg total every two weeks

Number of subjects in period 1	Praluent arm	Repatha arm
Started	15	15
Completed	12	12
Not completed	3	3
wrong administration	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	2	2

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	30	30	
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			
median	64		
inter-quartile range (Q1-Q3)	50 to 70	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	15	15	

End points

End points reporting groups

Reporting group title	Praluent arm
Reporting group description:	
no PCSK9-inhibitor at baseline, start of PCSK9 inhibition thearpy directly after baseline-visit. visite 1 (~2 weeks after baseline-visit), visit 2 (~12 weeks after baseline visit)	
Reporting group title	Repatha arm
Reporting group description:	
12 weeks Repatha	

Primary: Estimation of the fractional catabolic rate (FCR) of Apolipoprotein B in LDL

End point title	Estimation of the fractional catabolic rate (FCR) of Apolipoprotein B in LDL
End point description:	
This FCR is estimated using a mathematical model based on lipid-compositions of in the lipoproteinfractions VLDL, IDL, LDL and HDL. It results from the expected TG loss and the observed TG number per ApoB in LDL.	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	Praluent arm	Repatha arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: pools/day				
median (inter-quartile range (Q1-Q3))				
baseline	0.0215 (0.0165 to 0.0358)	0.0215 (0.0165 to 0.0358)		
2 weeks	0.0455 (0.0224 to 0.0909)	0.0455 (0.0224 to 0.0909)		
12 weeks	0.0467 (0.0274 to 0.1074)	0.0467 (0.0274 to 0.1074)		

Statistical analyses

Statistical analysis title	FCR
Statistical analysis description:	
Change in FCR before (baseline) and after (12 weeks) treatment with PCSK9-inhibitor	
Comparison groups	Repatha arm v Praluent arm

Number of subjects included in analysis	26
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	= 0.000378 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Change in FCR before (baseline) and after (12 weeks) treatment with PCSK9-inhibitor
Wilcoxon signed rank test
[2] - The fractional catabolic rate (derived using a mathematical model) increases significantly due to therapy with PCSK9-inhibitors. This is in accordance with intuition

Secondary: Cholesterol ester in HDL

End point title	Cholesterol ester in HDL

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Praluent arm	Repatha arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
baseline	37.97 (32.1 to 47.1)	41.1 (33 to 52.3)		
12 weeks	38.2 (32.6 to 47.9)	40.5 (31.7 to 51.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: TG in HDL

End point title	TG in HDL

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Praluent arm	Repatha arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
baseline	10 (9 to 11)	10 (8 to 13)		
12 weeks	10 (9 to 11)	11 (8 to 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cholesterol ester in LDL

End point title	Cholesterol ester in LDL

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Praluent arm	Repatha arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
baseline	105 (82 to 113)	109 (97 to 160)		
12 weeks	50 (34 to 67)	65 (31 to 81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Triglycerides in LDL

End point title	Triglycerides in LDL

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Praluent arm	Repatha arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
baseline	22 (20 to 25)	23 (20 to 33)		
12 weeks	16 (10 to 18)	17 (12 to 22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cholesterol ester in VLDL

End point title	Cholesterol ester in VLDL

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Praluent arm	Repatha arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
baseline	21 (9 to 30)	19 (10 to 27)		
12 weeks	12 (8 to 20)	11 (8 to 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Triglycerides in VLDL

End point title	Triglycerides in VLDL

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Praluent arm	Repatha arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
baseline	96 (46 to 197)	119 (48 to 126)		
12 weeks	73 (54 to 136)	71 (53 to 83)		

Statistical analyses

No statistical analyses for this end point

Secondary: ApoB in LDL

End point title	ApoB in LDL

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Praluent arm	Repatha arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
baseline	83 (72 to 98)	95 (81 to 126)		
12 weeks	47 (35 to 57)	58 (30 to 73)		

Statistical analyses

No statistical analyses for this end point

Secondary: ApoB in VLDL

End point title	ApoB in VLDL

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Praluent arm	Repatha arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
baseline	14 (7 to 19)	10 (7 to 15)		
12 weeks	15 (8 to 19)	9 (7 to 11)		

Statistical analyses

No statistical analyses for this end point

Secondary: ApoA1 in HDL

End point title	ApoA1 in HDL

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Praluent arm	Repatha arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mg/dl				
median (inter-quartile range (Q1-Q3))				
baseline	105 (93 to 113)	112 (98 to 139)		
12 weeks	107 (95 to 130)	106 (93 to 146)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	overall arm
Reporting group description: no PCSK9-inhibitor at baseline, start of PCSK9 inhibition thearpy directly after baseline-visit. visite 1 (~2 weeks after baseline-visit), visit 2 (~12 weeks after baseline visit)	

Serious adverse events	overall arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	overall arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 30 (13.33%)		
General disorders and administration site conditions			
Headache			
subjects affected / exposed[1]	1 / 1 (100.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed[2]	1 / 1 (100.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
itching, heat in the face			
alternative assessment type: Non-systematic			

subjects affected / exposed[3]	1 / 1 (100.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
muscle pain, skin rash			
subjects affected / exposed[4]	1 / 1 (100.00%)		
occurrences (all)	1		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: I have to admit, that I do not unterstand the warning (neither do I understand the difference between 'exposed' and 'affected').
However, there was only one case of that specific non-SAE in our study.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: I have to admit, that I do not unterstand the warning (neither do I understand the difference between 'exposed' and 'affected').
However, there was only one case of that specific non-SAE in our study.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: I have to admit, that I do not unterstand the warning (neither do I understand the difference between 'exposed' and 'affected').
However, there was only one case of that specific non-SAE in our study.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: I have to admit, that I do not unterstand the warning (neither do I understand the difference between 'exposed' and 'affected').
However, there was only one case of that specific non-SAE in our study.

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30670016