Clinical trial results:
A phase II multicenter trial with Rivaroxaban in the treatment of livedoid vasculopathy assessing the pain on a visual analog scale (VAS)

Summary

EudraCT number	2012-000108-13
Trial protocol	DE
Global end of trial date	11 September 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	UKM10_0018

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Münster
Sponsor organisation address	Albert-Schweitzer-Campus 1, Gebäude D5, Münster, Germany, 48149
Public contact	Klinik für Hautkrankheiten, Universitätsklinikum Münster, tobias.goerge@ukmuenster.de
Scientific contact	Klinik für Hautkrankheiten, Universitätsklinikum Münster, tobias.goerge@ukmuenster.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	11 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2014
Global end of trial reached?	Yes
Global end of trial date	11 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is the statistical evaluation of the therapeutic effects of rivaroxaban in patients with livedoid vasculopathy.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines in Good Clinical Practice. The study was not started before the competent ethics committee had given a favorable opinion. Written informed consent was obtained from all patients and the study was only conducted as approved by the Ethics committee and the competent authority. Amendments were only implemented after approval.

Background therapy:

Enoxaparin (1 mg/kg bodyweight) was allowed as backup medication in case of treatment failure.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	28 December 2012
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: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	18
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited for the study from four university hospitals throughout Germany. The recruitment period was from December 2012 to May 2014.

Pre-assignment

Screening details:

Eligible patients were at least 18 years of age with confirmed diagnosis of livedoid vasculopathy and 40 points on the pain visual analogue scale. All patients were required to have a wash out phase of any previous treatment of at least 24 hours before study medication was administered. Patients with symptomatic bleeding disorders were excluded.

Pre-assignment period milestones

Number of subjects started	28
Number of subjects completed	25

Pre-assignment subject non-completion reasons

Reason: Number of subjects	violation of inclusion criteria: 2
Reason: Number of subjects	lack of compliance: 1

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rivaroxaban - Baseline

Arm description:

Patients at baseline (before rivaroxaban treatment was initiated).

Arm type	Experimental
Investigational medicinal product name	Xarelto 10 mg
Investigational medicinal product code	
Other name	Rivaroxaban
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were treated orally with rivaroxaban at an initial dose of 10 mg twice daily and it was reduced to 10 mg once daily when pain decreased. It was also possible to initiate the treatment with a dose of 10 mg once daily. In case of insufficient pain reduction, rivaroxaban was increased to 10 mg twice daily.

Number of subjects in period 1[1]	Rivaroxaban - Baseline
Started	25
Completed	21
Not completed	4
Consent withdrawn by subject	1
Protocol deviation	2
lack of compliance	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: 28 Patients were enrolled in the study and were allocated for treatment with rivaroxaban. But three of the patients dropped out before the baseline examination because of violation of inclusion criteria (2 patients) or lack of compliance (1 patient). Therefore, only 25 patients started the baseline period.

Period 2

Period 2 title	Week 4
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rivaroxaban - Week 4

Arm description:

Patients who received rivaroxaban for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Xarelto 10 mg
Investigational medicinal product code	
Other name	Rivaroxaban
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were treated orally with rivaroxaban at an initial dose of 10 mg twice daily and it was reduced to 10 mg once daily when pain decreased. It was also possible to initiate the treatment with a dose of 10 mg once daily. In case of insufficient pain reduction, rivaroxaban was increased to 10 mg twice daily.

Number of subjects in period 2	Rivaroxaban - Week 4
Started	21
Completed	20
Not completed	1
Adverse event, non-fatal	1

Period 3

Period 3 title	Week 8
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rivaroxaban - Week 8

Arm description:

Patients who received rivaroxaban for 8 weeks.

Arm type	Experimental
Investigational medicinal product name	Xarelto 10 mg
Investigational medicinal product code	
Other name	Rivaroxaban
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were treated orally with rivaroxaban at an initial dose of 10 mg twice daily and it was reduced to 10 mg once daily when pain decreased. It was also possible to initiate the treatment with a dose of 10 mg once daily. In case of insufficient pain reduction, rivaroxaban was increased to 10 mg twice daily.

Number of subjects in period 3	Rivaroxaban - Week 8
Started	20
Completed	20

Period 4

Period 4 title	Week 12
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rivaroxaban - Week 12

Arm description:

Patients who received rivaroxaban for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Xarelto 10 mg
Investigational medicinal product code	
Other name	Rivaroxaban
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were treated orally with rivaroxaban at an initial dose of 10 mg twice daily and it was reduced

to 10 mg once daily when pain decreased. It was also possible to initiate the treatment with a dose of 10 mg once daily. In case of insufficient pain reduction, rivaroxaban was increased to 10 mg twice daily.

Number of subjects in period 4	Rivaroxaban - Week 12
Started	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	25	25	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	16	16	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	52.84		
standard deviation	± 17.03	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	7	7	

End points

End points reporting groups

Reporting group title	Rivaroxaban - Baseline
Reporting group description:	
Patients at baseline (before rivaroxaban treatment was initiated).	
Reporting group title	Rivaroxaban - Week 4
Reporting group description:	
Patients who received rivaroxaban for 4 weeks.	
Reporting group title	Rivaroxaban - Week 8
Reporting group description:	
Patients who received rivaroxaban for 8 weeks.	
Reporting group title	Rivaroxaban - Week 12
Reporting group description:	
Patients who received rivaroxaban for 12 weeks.	
Subject analysis set title	Enoxaparin - Baseline to Week 12
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who reached the end of the study (week 12) and needed backup treatment with enoxaparin.	

Primary: change in local pain between baseline and week 12

End point title	change in local pain between baseline and week 12
End point description:	
The primary endpoint is the change in local pain measured on a visual analogue scale (VAS) between baseline and week 12.	
End point type	Primary
End point timeframe:	
baseline and week 12	

End point values	Rivaroxaban - Baseline	Rivaroxaban - Week 12		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[1]	20[2]		
Units: visual analogue scale (VAS) score				
median (inter-quartile range (Q1-Q3))	65 (52 to 78)	6 (1 to 14)		

Notes:

[1] - Endpoint could be assessed only for 20 patients, because 5 patients had dropped out before week 12.

[2] - Endpoint could be assessed only for 20 patients, because 5 patients had dropped out before week 12.

Statistical analyses

Statistical analysis title	primary statistical analysis
Statistical analysis description:	
The primary analysis was performed with a significance level of α = 0.05. The null hypothesis was tested with a two-sided Wilcoxon test for paired data. It was conducted according to the ITT principle and is considered confirmatory. Therapeutic effectiveness was considered clinically relevant with a mean effect size in the primary endpoint of at least Δ/σ=0.7. A minimum sample size of 20 evaluable patients was necessary to demonstrate a significant therapeutic effect with a power of 80%.	
Comparison groups	Rivaroxaban - Baseline v Rivaroxaban - Week 12

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	2-sided exact Wilcoxon test
Parameter estimate	Median difference (net)
Point estimate	62.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	41.89
upper limit	68.81

Secondary: change in local pain between baseline and week 4

End point title	change in local pain between baseline and week 4

End point description:

The secondary endpoint is the change in local pain measured on a visual analogue scale (VAS) between baseline and week 4.

End point type	Secondary

End point timeframe:

baseline and week 4

End point values	Rivaroxaban - Baseline	Rivaroxaban - Week 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[3]	21[4]		
Units: visual analogue scale (VAS) score				
median (inter-quartile range (Q1-Q3))	65 (52 to 78)	20 (9 to 30)		

Notes:

[3] - Endpoint could be assessed only for 21 patients, because 4 patients had dropped out before week 4.

[4] - Endpoint could be assessed only for 21 patients, because 4 patients had dropped out before week 4.

Statistical analyses

Statistical analysis title	secondary statistical analysis

Statistical analysis description:

Secondary endpoints were analyzed partly descriptively. In case of inductive analyses, two-sided Wilcoxon test for paired data were used and data were analyzed according to the intention-to-treat principle. These analyses are considered exploratory and are interpreted accordingly.

Comparison groups	Rivaroxaban - Baseline v Rivaroxaban - Week 4
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	2-sided exact Wilcoxon test

Secondary: change in local pain between baseline and week 8

End point title	change in local pain between baseline and week 8

End point description:

The secondary endpoint is the change in local pain measured on a visual analogue scale (VAS) between baseline and week 8.

End point type	Secondary

End point timeframe:

baseline and week 8

End point values	Rivaroxaban - Baseline	Rivaroxaban - Week 8		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[5]	20[6]		
Units: visual analogue scale (VAS) score				
median (inter-quartile range (Q1-Q3))	65 (52 to 78)	10 (2.5 to 21)		

Notes:

[5] - Endpoint could be assessed only for 20 patients, because 5 patients had dropped out before week 8.

[6] - Endpoint could be assessed only for 20 patients, because 5 patients had dropped out before week 8.

Statistical analyses

Statistical analysis title	secondary statistical analysis

Statistical analysis description:

Secondary endpoints were analyzed partly descriptively. In case of inductive analyses, two-sided Wilcoxon test for paired data were used and data were analyzed according to the intention-to-treat principle. These analyses are considered exploratory and are interpreted accordingly.

Comparison groups	Rivaroxaban - Baseline v Rivaroxaban - Week 8
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	2-sided exact Wilcoxon test

Secondary: change in quality of life between baseline and week 4

End point title	change in quality of life between baseline and week 4

End point description:

The secondary endpoint is the change in quality of life measured with a Dermatology Life Quality Index (DLQI) questionnaire between baseline and week 4.

End point type	Secondary

End point timeframe:

baseline and week 4

End point values	Rivaroxaban - Baseline	Rivaroxaban - Week 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[7]	21[8]		
Units: DLQI Score				
arithmetic mean (standard deviation)	14.2 (± 6.93)	10.9 (± 6.76)		

Notes:

[7] - Endpoint could be assessed only for 21 patients, because 4 patients had dropped out before week 4.
[8] - Endpoint could be assessed only for 21 patients, because 4 patients had dropped out before week 4.

Statistical analyses

Statistical analysis title	secondary statistical analysis

Statistical analysis description:

Secondary endpoints were analyzed partly descriptively. In case of inductive analyses, two-sided Wilcoxon test for paired data were used and data were analyzed according to the intention-to-treat principle. These analyses are considered exploratory and are interpreted accordingly.

Comparison groups	Rivaroxaban - Baseline v Rivaroxaban - Week 4
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	2-sided exact Wilcoxon test

Secondary: change in quality of life between baseline and week 8

End point title	change in quality of life between baseline and week 8

End point description:

The secondary endpoint is the change in quality of life measured with a Dermatology Life Quality Index (DLQI) questionnaire between baseline and week 8.

End point type	Secondary

End point timeframe:

baseline and week 8

End point values	Rivaroxaban - Baseline	Rivaroxaban - Week 8		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[9]	20[10]		
Units: DLQI Score				
arithmetic mean (standard deviation)	14.2 (± 6.93)	8.25 (± 6.84)		

Notes:

[9] - Endpoint could be assessed only for 20 patients, because 5 patients had dropped out before week 8.
[10] - Endpoint could be assessed only for 20 patients, because 5 patients had dropped out before week

8.

Statistical analyses

Statistical analysis title	secondary statistical analysis

Statistical analysis description:

Secondary endpoints were analyzed partly descriptively. In case of inductive analyses, two-sided Wilcoxon test for paired data were used and data were analyzed according to the intention-to-treat principle. These analyses are considered exploratory and are interpreted accordingly.

Comparison groups	Rivaroxaban - Baseline v Rivaroxaban - Week 8
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	2-sided exact Wilcoxon test

Secondary: change in quality of life between baseline and week 12

End point title	change in quality of life between baseline and week 12

End point description:

The secondary endpoint is the change in quality of life measured with a Dermatology Life Quality Index (DLQI) questionnaire between baseline and week 12.

End point type	Secondary

End point timeframe:

baseline and week 12

End point values	Rivaroxaban - Baseline	Rivaroxaban - Week 12		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[11]	20[12]		
Units: DLQI Score				
arithmetic mean (standard deviation)	14.2 (± 6.93)	5.8 (± 4.95)		

Notes:

[11] - Endpoint could be assessed only for 20 patients, because 5 patients had dropped out before week 12.

[12] - Endpoint could be assessed only for 20 patients, because 5 patients had dropped out before week 12.

Statistical analyses

Statistical analysis title	secondary statistical analysis

Statistical analysis description:

Secondary endpoints were analyzed partly descriptively. In case of inductive analyses, two-sided Wilcoxon test for paired data were used and data were analyzed according to the intention-to-treat principle. These analyses are considered exploratory and are interpreted accordingly.

Comparison groups	Rivaroxaban - Baseline v Rivaroxaban - Week 12

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	2-sided exact Wilcoxon test

Secondary: Consumption of rescue medication - use of injections

End point title	Consumption of rescue medication - use of injections

End point description:

The secondary endpoint is the use of enoxaparin injections from baseline to week 12.

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	Enoxaparin - Baseline to Week 12			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: injections				
median (inter-quartile range (Q1-Q3))	19 (3 to 60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of rescue medication - duration of administration

End point title	Consumption of rescue medication - duration of administration

End point description:

The secondary endpoint is the duration of enoxaparin administration from baseline to week 12.

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	Enoxaparin - Baseline to Week 12			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: days				
median (inter-quartile range (Q1-Q3))	13 (3 to 30)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment in the study to week 12 (reported adverse events were followed up after week 12).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Safety group

Reporting group description:

Adverse Events were evaluated descriptively according to the as-treated principle.

Serious adverse events	Safety group		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 25 (12.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Superinfection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 25 (56.00%)		
Investigations			
Heart rate increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nervous system disorders			
Head discomfort			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	5		
Paraesthesia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Reproductive system and breast disorders			

Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Menorrhagia subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 4		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Dry mouth subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Gingival bleeding subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Respiratory, thoracic and mediastinal disorders Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2		
Petechiae subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Pruritus subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Psychiatric disorders Nervousness			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Limb discomfort			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Tendon pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Infections and infestations			
Herpes virus infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2013	The protocol was amended to add and modify some exclusion criteria and to modify the administration of the study medication in terms of initial dosing. At the beginning of the trial, the treatment was initiated with 10 mg rivaroxaban orally twice daily and was reduced to 10 mg orally once daily when pain decreased. After the amendment, the treatment was initiated with 10 mg rivaroxaban orally once daily and only in case of insufficient pain reduction, rivaroxaban was increased to 10 mg twice daily.

Notes:

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/26853646