



Clinical trial results: Effect of Bevacizumab Nasal Spray on Epistaxis Duration in Hereditary Hemorrhagic Telangiectasia (ALEGORI)

Summary

EudraCT number	2013-004204-19
Trial protocol	FR
Global end of trial date	07 September 2015

Results information

Result version number	v1 (current)
This version publication date	30 June 2021
First version publication date	30 June 2021

Trial information

Trial identification

Sponsor protocol code	2013-827
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02106520
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hospices Civils de Lyon
Sponsor organisation address	3 Quais des Célestins, Lyon, France, 69003
Public contact	Valérie Plattner, Hospices Civils de Lyon, +33 472406840, valerie.plattner@chu-lyon.fr
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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	30 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2015
Global end of trial reached?	Yes
Global end of trial date	07 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 3 different doses of bevacizumab administered as a nasal spray in a repeated manner for the duration of nosebleeds in patients with HHT.

Protection of trial subjects:

Regular DSMB meeting, all patients have been informed and have signed a consent form

Background therapy:

hereditary hemorrhagic telangiectasia (HHT)

Evidence for comparator: -

Actual start date of recruitment	01 April 2014
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	France: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	48
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients will be included in the study at the reference center for HHT in Lyon (principal investigator and coordinator) and at 4 skill centers distributed over French territory

Pre-assignment

Screening details:

Patients were included after checking inclusion/non-inclusion criteria

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bevacizumab 25mg

Arm description:

Three administrations of 25 mg of Bevacizumab spaced of 14 days

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Three administrations of 25 mg of Bevacizumab spaced of 14 days

Arm title	Bevacizumab 50mg
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Arm description:

Three administrations of 50 mg of Bevacizumab spaced of 14 days

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Three administrations of 50 mg of Bevacizumab spaced of 14 days

Arm title	Bevacizumab 75mg
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Arm description:

Three administrations of 75 mg of Bevacizumab spaced of 14 days

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Three administrations of 75 mg of Bevacizumab spaced of 14 days

Arm title	Placebo
Arm description:	
Three administrations of placebo spaced of 14 days	
Arm type	Placebo
Investigational medicinal product name	sodium chloride.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Three administrations of placebo spaced of 14 days

Number of subjects in period 1	Bevacizumab 25mg	Bevacizumab 50mg	Bevacizumab 75mg
Started	20	20	19
Completed	19	18	19
Not completed	1	2	0
Lost to follow-up	1	-	-
Protocol deviation	-	2	-

Number of subjects in period 1	Placebo
Started	21
Completed	19
Not completed	2
Lost to follow-up	2
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	Phase II
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Reporting group description: -

Reporting group values	Phase II	Total	
Number of subjects	80	80	
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)	48	48	
From 65-84 years	32	32	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	37	37	
Male	43	43	

End points

End points reporting groups

Reporting group title	Bevacizumab 25mg
Reporting group description:	
Three administrations of 25 mg of Bevacizumab spaced of 14 days	
Reporting group title	Bevacizumab 50mg
Reporting group description:	
Three administrations of 50 mg of Bevacizumab spaced of 14 days	
Reporting group title	Bevacizumab 75mg
Reporting group description:	
Three administrations of 75 mg of Bevacizumab spaced of 14 days	
Reporting group title	Placebo
Reporting group description:	
Three administrations of placebo spaced of 14 days	

Primary: monthly mean epistaxis duration

End point title	monthly mean epistaxis duration
End point description:	
End point type	Primary
End point timeframe:	
Before and after treatment	

End point values	Bevacizumab 25mg	Bevacizumab 50mg	Bevacizumab 75mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	19	21
Units: minute				
arithmetic mean (standard deviation)				
Before treatment	285.5 (± 433.4)	229.0 (± 215.9)	272.9 (± 396.6)	262.8 (± 230.4)
After treatment	259.2 (± 378.4)	244.0 (± 346.6)	215.0 (± 232.8)	200.4 (± 201.4)

Statistical analyses

Statistical analysis title	Intermediary principal outcome (25mg vs placebo)
Comparison groups	Placebo v Bevacizumab 25mg

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	t-test, 2-sided
Parameter estimate	Log odds ratio
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	1.17
Variability estimate	Standard deviation

Statistical analysis title	Intermediary principal outcome (50mg vs placebo)
Comparison groups	Placebo v Bevacizumab 50mg
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	t-test, 2-sided
Parameter estimate	Log odds ratio
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	1.15
Variability estimate	Standard deviation

Statistical analysis title	Intermediary principal outcome (75mg vs placebo)
Comparison groups	Placebo v Bevacizumab 75mg
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	t-test, 2-sided
Parameter estimate	Log odds ratio
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.1
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 months after treatment

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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Reporting groups

Reporting group title	Bevacizumab 25mg
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Reporting group description: -

Reporting group title	Bevacizumab 50 mg
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Reporting group description: -

Reporting group title	Bevacizumab 75mg
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Bevacizumab 25mg	Bevacizumab 50 mg	Bevacizumab 75mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)	4 / 20 (20.00%)	4 / 19 (21.05%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ulna fracture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 19 (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
Respiratory, thoracic and mediastinal			

disorders			
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Post sclerosis varice complication			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right leg infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	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	6 / 21 (28.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Ulna fracture			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foot fracture			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Post sclerosis varice complication			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Right leg infection			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Non-serious adverse events	Bevacizumab 25mg	Bevacizumab 50 mg	Bevacizumab 75mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 20 (70.00%)	10 / 20 (50.00%)	12 / 19 (63.16%)
Investigations			
Weight loss poor			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Dyspnoea exertional			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 20 (15.00%)	1 / 20 (5.00%)	1 / 19 (5.26%)
occurrences (all)	4	1	1
Sciatica			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ophthalmic migraine			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Dizziness			
subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Epigastric discomfort			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Aphthous ulcer			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Nasal injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Cystitis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Urinary tract infection			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Bronchitis			

subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	3 / 19 (15.79%)
occurrences (all)	1	0	3
Erysipelas			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
cardiac pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Tracheitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 21 (76.19%)		
Investigations			
Weight loss poor			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Dyspnoea exertional			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Cardiac disorders			

Extrasystoles subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Sciatica subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Ophthalmic migraine subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Pain subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Ear and labyrinth disorders Dizziness subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Epigastric discomfort subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Diarrhoea			

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Aphthous ulcer subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Reproductive system and breast disorders Prostatitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Nasal injury subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Infections and infestations Cystitis subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
Bronchitis subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Erysipelas subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Rectal haemorrhage subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		

Sinusitis			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
cardiac pain			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Tracheitis			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		

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/27599328>