Clinical trial results:
EFFECT OF BEVACIZUMAB SUBCONJUNCTIVAL INJECTIONS ON CORNEAL NEWVESSELS

Summary

EudraCT number	2010-022858-16
Trial protocol	FR
Global end of trial date	13 April 2018

Results information

Result version number	v1 (current)
This version publication date	03 May 2021
First version publication date	03 May 2021
Summary attachment (see zip file)	Summary of the final report (BECONNEC-resume rapport final.pdf)

Trial information

Trial identification

Sponsor protocol code	I07034

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01501760
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU de Limoges
Sponsor organisation address	2 Avenue MArtin Luther KING, Limoges, France, 87000
Public contact	DR A BENTALEB, CHU de Limoges, 33 0555058616, abdeslam.bentaleb@chu-limoges.fr
Scientific contact	Pr Pierre Yves ROBERT, CHU de Limoges, 33 05 55 05 62 31, pierre-yves.robert@unilim.fr-limoges.fr

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	17 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate Bevacizumab subconjunctival injections effectiveness on corneal neovascularisation reduction after 3 monthly injections

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable French statutes and regulations regarding ethical committee review,competent authority , informed consent, and the protection of human subjects participating in biomedical research.
Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject .
During this pre-inclusion visit, investigator informs the patient and answers all his questions concerning the objective, the nature of the constraints, the foreseeable risks and the expected benefits of the research. It also specifies the patient's rights in the context of biomedical research. After this information session, the patient has a reflection period.
In addition, a DSMB has been set up to supervise the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2011
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: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	23
From 65 to 84 years	14
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 study centers in FRance between 03/02/2012 (first subject first visit) and 12/09/2017 (last subject last visit).

Pre-assignment

Screening details:

A total of 38 subjects were enrolled, received treatment and completed the study.

Period 1

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

Blinding implementation details:

The syringes prepared at the pharmacy (bevacizumab or placebo), will be presented in a strictly identical manner. The labeling of the syringes will ensure that the doctor and the patient are not aware of it.

Arms

Are arms mutually exclusive?	Yes
Arm title	BEVACIZUMAB

Arm description:

Subjects received 1 subconjunctival injection of 0.2 ml of Bevacizumab (i.e. 5 mg) to be repeated twice, 1 month apart, i.e. 3 injections

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin*
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Conjunctival use

Dosage and administration details:

1 subconjunctival injection of 0.2 ml of Bevacizumab (i.e. 5 mg)

Arm title	PLACEBO

Arm description:

Subjects received 1 subconjunctival injection of 0f 0.2 ml of 0.9% NaCl to be repeated twice, 1 month apart, i.e. 3 injections

Arm type	Placebo
Investigational medicinal product name	PLacebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subconjunctival use

Dosage and administration details:

Dosage: 1 subconjunctival injection of 0.2 ml of 0.9% NaCl
Ready-to-use pre-filled syringe prepared at the pharmacy of the investigating center

Number of subjects in period 1	BEVACIZUMAB	PLACEBO
Started	20	18
Completed	20	18

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	38	38	
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	57.5		
standard deviation	± 18.1	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	25	25	

End points

End points reporting groups

Reporting group title	BEVACIZUMAB
Reporting group description:	
Subjects received 1 subconjunctival injection of 0.2 ml of Bevacizumab (i.e. 5 mg) to be repeated twice, 1 month apart, i.e. 3 injections	
Reporting group title	PLACEBO
Reporting group description:	
Subjects received 1 subconjunctival injection of 0f 0.2 ml of 0.9% NaCl to be repeated twice, 1 month apart, i.e. 3 injections	

Primary: Subconjunctival injections effectiveness at month 3

End point title	Subconjunctival injections effectiveness at month 3
End point description:	
The outcome measure associated with this primary objective is the efficacy of Bevacizumab administered by the subconjunctival route in reducing corneal neovascularization. It was evaluated by comparing in each group the proportion of responder patients defined by a percentage of corneal surface area occupied by neovessels at 3 months reduced by more than 30%, evaluated on photos by surface measurement software.	
End point type	Primary
End point timeframe:	
After 3 injections (3 month)	

End point values	BEVACIZUMAB	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: Percentage of subjects				
arithmetic mean (standard deviation)	-8.6 (± 32.8)	2.6 (± 20.8)		

Statistical analyses

Statistical analysis title	Treatment difference
Statistical analysis description:	
This end point was evaluated by comparing in each group the proportion of responder patients defined by a percentage of corneal surface area occupied by neovessels at 3 months reduced by more than 30%, evaluated on photos by software for measuring surfaces according to a pre-established scale. The statistical analysis associated with this primary objective consisted of a Fisher exact test	
Comparison groups	PLACEBO v BEVACIZUMAB

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5284
Method	Fisher exact

Secondary: Effectiveness of Bevacizumab at Month 6

End point title	Effectiveness of Bevacizumab at Month 6

End point description:

To evaluate the effectiveness of Bevacizumab, a on the proportion of responder patients compared to a placebo at 6 months .
The judgment criterion associated with this secondary objective was the patient's response at 6 months (the percentage of corneal surface area occupied by neovessels at 6 months is compared between the two groups)
The statistical analysis associated consisted of Fisher's exact test.

End point type	Secondary

End point timeframe:

At month 6

End point values	BEVACIZUMAB	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: Percentage of subjects				
arithmetic mean (standard deviation)	-6.1 (± 32.5)	1 (± 27.6)		

Statistical analyses

Statistical analysis title	Treatment difference at month 6
Comparison groups	PLACEBO v BEVACIZUMAB
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7625
Method	Fisher exact

Secondary: The effectiveness of bevacizumab on reducing the use of corneal graft

End point title	The effectiveness of bevacizumab on reducing the use of corneal graft

End point description:

The outcome measure associated with this secondary objective was the proportion of patients with indication of keratoplasty at 6 months.
The statistical analysis associated with this secondary objective 2 consisted of a Chi² test.

End point type	Secondary

End point timeframe:
At month 6

End point values	BEVACIZUMAB	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	16		
Units: Number of subjects	7	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	BEVACIZUMAB

Reporting group description:

Subjects received 1 subconjunctival injection of 0.2 ml of Bevacizumab (i.e. 5 mg) to be repeated twice, 1 month apart, i.e. 3 injections

Reporting group title	PLACEBO

Reporting group description:

- 0.9% sodium chloride
- ready-to-use pre-filled syringe prepared at the pharmacy of the investigating center CHU
- Dosage: 1 subconjunctival injection of 0.2 ml of 0.9% NaCl to be repeated twice, 1 month apart, i.e. 3 injections

Serious adverse events	BEVACIZUMAB	PLACEBO	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	BEVACIZUMAB	PLACEBO	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)	15 / 18 (83.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 20 (25.00%)	2 / 18 (11.11%)	
occurrences (all)	6	2	
General disorders and administration site conditions			
Injection site pain			

subjects affected / exposed	9 / 20 (45.00%)	4 / 18 (22.22%)	
occurrences (all)	19	8	
Eye disorders			
Lacrimal disorder			
subjects affected / exposed	5 / 20 (25.00%)	6 / 18 (33.33%)	
occurrences (all)	6	8	
Visual acuity reduced			
subjects affected / exposed	5 / 20 (25.00%)	5 / 18 (27.78%)	
occurrences (all)	4	4	
Pain			
subjects affected / exposed	11 / 20 (55.00%)	8 / 18 (44.44%)	
occurrences (all)	17	12	
Hyperthermia			
subjects affected / exposed	6 / 20 (30.00%)	5 / 18 (27.78%)	
occurrences (all)	11	7	
Foreign body			
subjects affected / exposed	5 / 20 (25.00%)	4 / 18 (22.22%)	
occurrences (all)	6	6	
Conjunctival hemorrhage			
subjects affected / exposed	2 / 20 (10.00%)	6 / 18 (33.33%)	
occurrences (all)	4	7	
Photophobia			
subjects affected / exposed	6 / 20 (30.00%)	4 / 18 (22.22%)	
occurrences (all)	7	4	
Floating Glass Bodies			
subjects affected / exposed	5 / 20 (25.00%)	4 / 18 (22.22%)	
occurrences (all)	6	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2016	Recruitment has been a major problem since the start of the research despite a much larger number of "selected" patients (72% non-selection in Limoges for example). One of the obstacles stems from the application of the criterion of cardiovascular non-inclusion (Patient with unbalanced arterial hypertension and Patient with a history of stroke, myocardial infarction, angina, thrombophlebitis, Raynaud.). The relaxation of these 2 criteria would undoubtedly allow a better recruitment since no serious cardiovascular effect was identified in the 21 patients already included, the quantity of product injected locally is low and the current literature does not seem to demonstrate it. serious systemic cardiovascular effects after ocular injection of bevacizumab. Changes to non-inclusion criteria as follows: -Patient with unbalanced arterial hypertension -Patient with a history of an acute cardiovascular event less than 6 months old and / or progressive such as stroke, myocardial infarction, thrombophlebitis -Patient with a history of angina, Raynaud's syndrome considered unstable This amendment, apppuived by trhe DSMB, has been submitted and approved by the Ethic committee and the Competent authority.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 September 2017	The trial was terminated after 38 inclusions. Indeed, it has become very difficult to recruit new patients.	-

Notes:

Limitations and caveats

None reported