Clinical trial results:
Management of recurrent pterygium to prevent visual impairment (REPEAT)

Summary

EudraCT number	2015-003217-20
Trial protocol	GB
Global end of trial date	11 April 2018

Results information

Result version number	v1 (current)
This version publication date	25 April 2019
First version publication date	25 April 2019

Trial information

Trial identification

Sponsor protocol code	15073

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02530801
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	Jubilee Campus, Triumph Road, Nottingham, United Kingdom, NG8 1DH
Public contact	Harminder Dua, University of Nottingham, 0115 9709796, harminder.dua@nottingham.ac.uk
Scientific contact	Harminder Dua, University of Nottingham, 0115 8467906, sponsor@nottingham.ac.uk

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	04 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 April 2018
Global end of trial reached?	Yes
Global end of trial date	11 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of combined 5FU and Avastin injections in the treatment of recurrent pterygium.

Protection of trial subjects:

Pregnant women, women aiming for conception, and nursing mothers were excluded from the study. Patients under 18 years of age were also excluded. Dose adjustment was not expected to be needed for patients with renal or hepatic impairment. There is no evidence in the literature that it affects spermatogenesis in men who are aiming to father a child. Therefore they were not excluded from the study but were informed that there is no evidence in the literature regarding whether Avastin® can affect sperm.

Participants were asked to contact the study site immediately in the event of any serious adverse event. History would be taken and recorded and meticulous eye examination done for the patient. All adverse events were recorded, appropriately treated and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator (delegated responsibility by the Sponsor) would be informed immediately (within 24 hours) of any serious adverse events and would determine seriousness and causality in conjunction with any treating medical practitioners.

All serious adverse events were to be recorded and reported to the MHRA and REC as part of the annual Development Safety Update Reports. SUSARs were to be reported within the statutory timeframes to the MHRA and REC as stated below.

Background therapy:

Antibiotic eye drops (chloramphenicol)

Evidence for comparator:

No comparator was used for this trial.

Actual start date of recruitment	01 December 2015
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	United Kingdom: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from specialist cornea and ocular surface clinics of Professor HS Dua at Nottingham University Hospitals NHS Trust between 10.01.2017 and 09.11.2017. The trial setting is a secondary care hospital in the UK.

Pre-assignment

Screening details:

Patient meets all eligibility criteria as per protocol including age over the age of 18, able to give informed consent, presenting with either early or recurrent pterygium, able to tolerate injection, not pregnant or breastfeeding or planning on becoming pregnant, do not have concurrent eye conditions that would make them unsuitable.

Period 1

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

Arms

Arm title	Treatment Group

Arm description:

Patients receiving Avastin and 5 flurouracil.

Arm type	Experimental
Investigational medicinal product name	5 Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subconjunctival use

Dosage and administration details:

0.15 ml of 5FU (3.75mg) administered into the body of the pterygium. Up to 5 injections at 5 visits could be given.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for injection
Routes of administration	Subconjunctival use

Dosage and administration details:

0.15 ml of Avastin® (3.75mg) administered in the body of the pterygium lesion. Up to 5 injections at 5 visits could be given.

Number of subjects in period 1	Treatment Group
Started	20
Completed	20

Period 2

Period 2 title	Post-injection series
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment Group

Arm description:

Patients receiving Avastin and 5 flurouracil.

Arm type	Experimental
Investigational medicinal product name	5 Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subconjunctival use

Dosage and administration details:

0.15 ml of 5FU (3.75mg) administered into the body of the pterygium. Up to 5 injections at 5 visits could be given.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for injection
Routes of administration	Subconjunctival use

Dosage and administration details:

0.15 ml of Avastin® (3.75mg) administered in the body of the pterygium lesion. Up to 5 injections at 5 visits could be given.

Number of subjects in period 2	Treatment Group
Started	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	Pre-injection

Reporting group description: -

Reporting group values	Pre-injection	Total	
Number of subjects	20	20	
Age categorical			
All participants were aged over 18, there was no upper age limit.			
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	4	4	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	54		
full range (min-max)	22 to 83	-	
Gender categorical			
Units: Subjects			
Female	8	8	
Male	12	12	
Type of pterygium			
Units: Subjects			
Primary	16	16	
Recurrent	4	4	
Total Number of Injections Received			
Units: Subjects			
1 injection	0	0	
2 injections	2	2	
3 injections	1	1	
4 injections	1	1	
5 injections	16	16	

End points

End points reporting groups

Reporting group title	Treatment Group
Reporting group description:	
Patients receiving Avastin and 5 flurouracil.	
Reporting group title	Treatment Group
Reporting group description:	
Patients receiving Avastin and 5 flurouracil.	

Primary: Arrest of progression and/or regression of thickness of the conjunctiva at the site of the lesion.

End point title	Arrest of progression and/or regression of thickness of the conjunctiva at the site of the lesion.
End point description:	
The response to treatment was judged clinically by biomicroscopy examination (when no further advance of the lesion was noted over three follow-up visits, 1-2 weeks apart) and quantitatively by comparison with pre-treatment slit lamp photographs (arrest of progression and/or regression of vascularity and thickness of the conjunctiva at the site of the lesion). The degree of vascularity and thickness of the conjunctiva was assessed using a semi- automatic method by comparison of the pre and post treatment digital eye photographs by two independent blind reviewers.	
End point type	Primary
End point timeframe:	
After a maximum of 5 injections of 5FU and Avastin over the course of six months	

End point values	Treatment Group	Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[1]	20[2]		
Units: microns				
arithmetic mean (full range (min-max))	323 (94 to 620)	285 (88 to 535)		

Notes:

[1] - 20 subjects were analysed pre and post their series of injections.

[2] - 20 subjects were analysed pre and post their series of injections.

Statistical analyses

Statistical analysis title	Reduction in thickness pre and post injection
Statistical analysis description:	
As this is a single arm trial the comparison groups are the 20 participants pre and post injection.	
Comparison groups	Treatment Group v Treatment Group

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0078
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	35.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.7
upper limit	59.9

Notes:

[3] - Comparison of pterygium thickness pre and post injection series.

Secondary: Disappearance of redness

End point title	Disappearance of redness

End point description:

Mean reduction in clinical grade post injection.

End point type	Secondary

End point timeframe:

After a maximum of five injections over a six month period.

End point values	Treatment Group	Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[4]	20[5]		
Units: Clinical scoring				
arithmetic mean (full range (min-max))	2.313 (2 to 3)	1.625 (1 to 3)		

Notes:

[4] - 20 subjects were analysed pre and post their series of injections.

[5] - 20 subjects were analysed pre and post their series of injections.

Statistical analyses

Statistical analysis title	Reduction in clinical grade pre and post injection
Comparison groups	Treatment Group v Treatment Group
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0004
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	2-sided
lower limit	0.367
upper limit	1.008

Notes:
[6] - Reduction in clinical grade pre and post injection

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 2 weeks post-injection.

Adverse event reporting additional description:

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Overall Trial

Reporting group description:

All participants who received Avastin and 5 Fluorouracil.

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

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

Non-serious adverse events	Overall Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)		
Eye disorders			
Superficial punctate keratitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2016	Primary pterygium was added to the inclusion criteria and the sample size was increased to 40. An additional co-investigator was added.
12 January 2017	A tissue collection sub-study was added to obtain consent from patients who received injections to use the pterygium tissue after being surgically excised, as surgical excision is the standard care in pterygium patients, and also from patients who have had injections as part of their normal standard of care outside the study as they may also have their residual pterygium excised. The tissue was to be examined to ascertain what effect the injections had on the pterygium. This tissue is normally sent to the laboratory for routine examination under the microscope. The tissue will be disposed of at the end of the study in accordance with the Human Tissue Act.
26 March 2018	Consent to be sought from participants that any remaining pterygium tissue samples may be stored and used in possible future research.
09 April 2018	Inclusion of the retrospective data of the patients who have already received the treatment in the protocol as part of their NHS standard care. Thirteen patients have already provided their consent, using the information sheet and consent form which talk about their prospective treatment, but it was clearly explained to them that they were consenting to the use of their retrospective data, where they have already received the trial treatment as part of their standard care.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although the recruitment target had been amended to 40, the decision was made to stop recruitment at 20 participants as sufficient data was collected to achieve the protocol objectives.

Notes: