Clinical trial results:
Prostaglandin F2-alpha eye drops (Bimatoprost) in thyroid eye disease: a randomised
controlled double blind crossover trial

Summary

EudraCT number	2014-000540-15
Trial protocol	GB
Global end of trial date	25 April 2016

Results information

Result version number	v1 (current)
This version publication date	17 April 2019
First version publication date	17 April 2019
Summary attachment (see zip file)	BIMA study abstract (BIMA Study abstract.pdf)

Trial information

Trial identification

Sponsor protocol code	SPON1266-14

Additional study identifiers

ISRCTN number	ISRCTN46696624
ClinicalTrials.gov id (NCT number)	NCT02059655
WHO universal trial number (UTN)	-
Other trial identifiers	NISCHR RESEARCH FOR PATIENT AND PUBLIC BENEFIT WAL: RFPPB-2012-1015, Research Ethics Committee: 14/WA/0081

Notes:

Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	Newport Road, Cardiff, United Kingdom, CF24 0DE
Public contact	Dr Shazli Draman, Cardiff University, 44 (0)29 208 79130, Shaw.C3@cardiff.ac.uk
Scientific contact	Dr Shazli Draman, Cardiff University, 44 (0)29 208 79130, Shaw.C3@cardiff.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	25 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2016
Global end of trial reached?	Yes
Global end of trial date	25 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective is to determine if PGF2α eye drops can reduce proptosis in inactive thyroid eye disease.

Protection of trial subjects:

The safety of Bimatoprost is already established in its use in other indications. However, preliminary risk assessments were conducted and the Trial Management Group routinely reviewed blinded adverse events on a three monthly basis. Since significant new adverse event information was not anticipated, a formal data safety monitoring board (DSMB) was not established. However, it was planned that if an unexpected rate of adverse event is observed, this will be discussed with the Trial Steering Committee and an independent DSMB would be convened to review unmasked data if considered appropriate.

Background therapy:

N/A

Evidence for comparator:

The placebo was an artificial tear. To enhance masking the placebo contained artificial tears with similar preservative (Benzalkonium chloride – marketed preparation) which replicated any mild stinging sensation experienced with Bimatoprost. Both products were relabelled by the trial pharmacist in accordance with EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 13.

Actual start date of recruitment	20 November 2014
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: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period from 20 November 2016 to 27 February 2015 in the UK. Single site study. A cross over study with the intention that all 31 patients recruited would take part in the IMP and placebo arms of the study with a washout period in between.

2 periods:
Overall trial: specify primary endpoint
Baseline period: not duplicated in above

Pre-assignment

Screening details:

Trial participants were identified from the database of the multidisciplinary thyroid eye disease clinic. The key eligibility criteria was for patients with stable proptosis for at least 6 months duration. Potential participants meeting the inclusion criteria were sent a letter informing them of the study and inviting their participation.

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, Monitor, Data analyst, Assessor

Blinding implementation details:

Placebo contained similar preservative as Bimatoprost to replicate the stinging sensation.
PI, ophthalmologists & assessors no access to eye drop bottles. Patients instructed not to bring their eye drop bottles to the eye clinic, but only to the hospital pharmacy at the end of each treatment phase for disposal.
Objective findings were recorded by the assessor (e.g. proptosis measurements).
Assessor had no access to prior assessment records/photos to compare with current measurements.

Arms

Are arms mutually exclusive?	No
Arm title	Bimatoprost

Arm description:

Prostaglandin F2-alpha eye drops

Arm type	Experimental
Investigational medicinal product name	Prostaglandin F2-alpha
Investigational medicinal product code	
Other name	Bimatoprost
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop per eye daily of Bimatoprost 0.03%

Arm title	Placebo

Arm description:

The placebo was an artificial tear. To enhance masking the placebo contained artificial tears with similar preservative (Benzalkonium chloride – marketed preparation) to replicate any stinging sensation experienced with Bimatoprost.

Arm type	Placebo

Investigational medicinal product name	Hypromellose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

1 drop per day

Number of subjects in period 1	Bimatoprost	Placebo
Started	31	31
Allocation to treatment/placebo	31	31
Washout period (2 months)	31	31
Allocation to placebo/treatment	30	30
Completed	30	30
Not completed	1	1
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Bimatoprost
Reporting group description:	
Prostaglandin F2-alpha eye drops	
Reporting group title	Placebo
Reporting group description:	
The placebo was an artificial tear. To enhance masking the placebo contained artificial tears with similar preservative (Benzalkonium chloride – marketed preparation) to replicate any stinging sensation experienced with Bimatoprost.	

Reporting group values	Bimatoprost	Placebo	Total
Number of subjects	31	31	31
Age categorical			
>18 years of age			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	23	23	23
From 65-84 years	8	8	8
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	55.2	55.2	
full range (min-max)	28 to 74	28 to 74	-
Gender categorical			
Both male & female			
Units: Subjects			
Female	26	26	26
Male	5	5	5
Smoking			
Smoking history at visit 1 and any changes in smoking habits documented throughout the trial.			
Units: Subjects			
Smoker			
Non / ex smoker			
Total diplopia			
Units: Subjects			
Intermittent			
Inconstant			
Constant			
Clinical activity score			
Units: Subjects			
CAS 0			

CAS 1 CAS 2 CAS 3			
BMI Units: kg/m2 arithmetic mean standard deviation	± 	± 	-
GO duration Units: years median inter-quartile range (Q1-Q3)	 	 	 -
Exophthalmometer Units: mm arithmetic mean standard deviation	 ±	 ±	 -
Palpebral aperture Units: mm arithmetic mean standard deviation	 ±	 ±	 -
FT4 Units: pmol/L median inter-quartile range (Q1-Q3)	 	 	 -
TSH Units: mU/L median inter-quartile range (Q1-Q3)	 	 	 -

Subject analysis sets

Subject analysis set title	Baseline
Subject analysis set type	Full analysis

Subject analysis set description:

This randomised controlled double blind crossover trial was conducted in a single tertiary care academic medical centre. Patients with longstanding, inactive GO but persistent proptosis (> 20 mm in at least one eye) were recruited. Allowing for a 15% dropout rate, 31 patients were randomized in order to identify a treatment effect of 2.0 mm (p=0.05, two-sided, power 0.88). Following informed consent, participants were randomized to receive Bimatoprost or placebo for three months after which they underwent a two-month washout, before switching to the opposite treatment. The primary outcome was to compare the change in exophthalmometry readings over the two 3-month treatment periods.

Reporting group values	Baseline		
Number of subjects	31		
Age categorical			
>18 years of age			
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)	23		
From 65-84 years	8		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	55.2		
full range (min-max)	28 to 74		
Gender categorical			
Both male & female			
Units: Subjects			
Female	26		
Male	5		
Smoking			
Smoking history at visit 1 and any changes in smoking habits documented throughout the trial.			
Units: Subjects			
Smoker	23		
Non / ex smoker	8		
Total diplopia			
Units: Subjects			
Intermittent	8		
Inconstant	5		
Constant	6		
Clinical activity score			
Units: Subjects			
CAS 0	21		
CAS 1	6		
CAS 2	4		
CAS 3	0		
BMI			
Units: kg/m2			
arithmetic mean	29		
standard deviation	± 6.5		
GO duration			
Units: years			
median	7.6		
inter-quartile range (Q1-Q3)	3.6 to 12.3		
Exophthalmometer			
Units: mm			
arithmetic mean	23.6		
standard deviation	± 2.5		
Palpebral aperture			
Units: mm			
arithmetic mean	11.1		
standard deviation	± 2.0		
FT4			
Units: pmol/L			
median	15.9		
inter-quartile range (Q1-Q3)	13.5 to 17.4		
TSH			
Units: mU/L			
median	0.87		

inter-quartile range (Q1-Q3)	0.12 to 2.6		

End points

End points reporting groups

Reporting group title	Bimatoprost
Reporting group description: Prostaglandin F2-alpha eye drops	
Reporting group title	Placebo
Reporting group description: The placebo was an artificial tear. To enhance masking the placebo contained artificial tears with similar preservative (Benzalkonium chloride – marketed preparation) to replicate any stinging sensation experienced with Bimatoprost.	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description: This randomised controlled double blind crossover trial was conducted in a single tertiary care academic medical centre. Patients with longstanding, inactive GO but persistent proptosis (> 20 mm in at least one eye) were recruited. Allowing for a 15% dropout rate, 31 patients were randomized in order to identify a treatment effect of 2.0 mm (p=0.05, two-sided, power 0.88). Following informed consent, participants were randomized to receive Bimatoprost or placebo for three months after which they underwent a two-month washout, before switching to the opposite treatment. The primary outcome was to compare the change in exophthalmometry readings over the two 3-month treatment periods.	

Primary: change in value

End point title	change in value
End point description: Data analysis will proceed according to CONSORT guidelines for randomised controlled trials. This will be conducted under guidance of senior statistician. The first stage of the analysis will be to use descriptive statistics to describe the group of individuals recruited to the trial in relation to those eligible, and to investigate comparability of the trial arms at baseline. A tabulation of demographic and clinical variables will be carried out to identify any chance imbalances at baseline between the two treatment groups The mean change in proptosis measurement in the treated phase and control phase will be compared with a paired t-test in the first instance. In order to protect the independence of the data points, this will be carried out using the mean improvement of the two eyes where both have been treated. In addition to this proptosis both eyes for patients with both eyes treated and the one eye for patients with only one treated eye will be analysed using a multilev	
End point type	Primary
End point timeframe: 3 months	

End point values	Bimatoprost	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: mm				
arithmetic mean (standard deviation)	0.17 (± 1.5)	0.26 (± 2.0)		

Attachments (see zip file)	Mean change in proptosis measurement /Figure 2.jpg

Statistical analyses

Statistical analysis title	paired t-test

Statistical analysis description:

The mean change in proptosis measurement in the placebo phase and Bimatoprost phase was compared with a paired t-test. This was carried out using the mean improvement of the two eyes where both have been treated or the change in one eye where only one was treated. Multilevel model in STATA version 12 using demographic and clinical variables (including baseline, the order of treatment and carryover effects) was also used to adjust for unexplained variance and obtain better estimates of effect s

Comparison groups	Placebo v Bimatoprost
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	paired t-test two-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.32
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: November 2014 - March 2016	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	3
Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

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	22 / 29 (75.86%)		
Surgical and medical procedures			
surgery - middle ear			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness postural			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
General disorders and administration site conditions			
Nasal cavity/paranasal sinus reactions			
subjects affected / exposed	7 / 29 (24.14%)		
occurrences (all)	9		
Pain - migraine / headache			

subjects affected / exposed	6 / 29 (20.69%)		
occurrences (all)	11		
Polydypsia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Ear and labyrinth disorders			
auditory ear			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Eye disorders			
Foreign body sensation			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Conjunctival hyperemia			
subjects affected / exposed	10 / 29 (34.48%)		
occurrences (all)	16		
Eye dryness			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Burning sensation			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Eye pruritus			
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	5		
Eyelid swelling			
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	5		
Conjunctivitis			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Difficulty eye opening			

subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Eye pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Eyelid pigmentation	Additional description: Dark skin patch right eye		
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Ptosis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Meibomian cyst			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Gastrointestinal disorders			
Diarrhoea and vomiting			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Heartburn/dyspepsia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Flu-like syndrome			
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	6		
Bronchospasm			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Urticaria	Additional description: eczema rash Prickly Heat generalised itchy skin		
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Renal and urinary disorders			

Urine colour change			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthritis non-spectic			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Frozen shoulder			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Plantar fasciitis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Pain back			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	5		
pain - chest wall			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Pain joint	Additional description: joint pain aching shoulders Sore shoulder muscle		
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Pain muscle			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Infections and infestations			
Infection	Additional description: throat infection chest infection Lt Ear infection Chesty cough chest infection Cold sore		
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2014	The original placebo (Hypromellose), detailed in the initial CT application, became unavailable. An alternative manufacturer of the same product, Hypromellose, was been found. The excipients in two manufacturer brands were exactly the same.

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/30880626