Clinical trial results:
Combined Immunosuppression and Radiotherapy in Thyroid Eye Disease

Summary

EudraCT number	2004-002547-27
Trial protocol	GB
Global end of trial date	31 December 2017

Results information

Result version number	v1 (current)
This version publication date	31 December 2020
First version publication date	31 December 2020
Summary attachment (see zip file)	Summary key variables (CIRTED SUMMARY.xls) Notes on CIRTED summary (Notes on the CIRTED Summary.docx)

Trial information

Trial identification

Sponsor protocol code	OP/CD001

Additional study identifiers

ISRCTN number	ISRCTN22471573
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Bristol
Sponsor organisation address	1 Cathedral Square, Bristol, United Kingdom, BS1 5DD
Public contact	Richard Lee, University of Bristol, +44 01173312020, richard.lee@bristol.ac.uk
Scientific contact	Richard Lee, University of Bristol, +44 01173312020, richard.lee@bristol.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	01 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Test the hypotheses that in patients being treated with prednisolone for active Thyroid Eye Disease:1.RADIOTHERAPY (compared with placebo) induces early remission and reduces long-term disease severity.2.COMBINED SYSTEMIC IMMUNOSUPPRESSION WITH ORAL AZATHIOPRINE (compared with placebo) reduces long-term disease severity.

Protection of trial subjects:

All treatments and assessments are used in routine NHS care, although substantial benefits of treatments were unclear. This trial was to assess whether either was superior and refine our knowledge of the potential benefits

Background therapy:

Oral steroids in a reducing regime, given to all participants

Evidence for comparator:

Factorial 2x2 design for radiotherapy and azathioprine. So radiotherapy was assessed against those not receiving radiotherapy. Azathioprine was assessed against those not receiving it. Interaction between azathioprine and radiotherapy was also assessed

Actual start date of recruitment	02 January 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 126
Worldwide total number of subjects	126
EEA total number of subjects	126

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)	113
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

People were recruited from London, Bristol, Manchester, Glasgow and Cardiff from NHS clinics.

Pre-assignment

Screening details:

Eligibility was clarified using Clinical Activity Score and other factors including proptosis. Pregnancy, previous use of radio-iodine or dysthyroid optic neuropathy as well as FBC or liver abnormalities were also reasons for exclusion

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Sham radiotherapy was used. Individuals in the placebo group also had random dose changes to maintain

Arms

Are arms mutually exclusive?	No
Arm title	Radiotherapy

Arm description:

Twenty gray (Gy) of radiation was administered to the retrobulbar orbit in 10-12 fractions over 2 to 3 weeks. Subjects receiving sham radiotherapy also attended and underwent all the same procedures other than no radiation being delivered.

Arm type	Factorial intervention
Investigational medicinal product name	Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor
Routes of administration	Route of administration not applicable

Dosage and administration details:

Twenty gray (Gy) of radiation was administered to the retrobulbar orbit in 10-12 fractions over 2 to 3 weeks.

Arm title	Azathioprine

Arm description:

Treatment dose varied between 100mg and 200mg daily (dispensed as 50 mg tablets), depending on body weight. Matched placebo tablets and packaging were used and the dose was adjusted according to a standard algorithm dependent on patient’s blood test results. Again, extensive effort was taken to ensure participants were unaware if they were receiving placebo, including identical blood tests and random placebo dose adjustments. To reduce the risk of serious adverse events, patients with abnormal TPMT activity who are at increased risk of developing bone marrow suppression (low activity) or hepatotoxicity (high activity) with azathioprine were not enrolled.

Arm type	factorial intervention
Investigational medicinal product name	Azathioprine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

See other section

Number of subjects in period 1	Radiotherapy	Azathioprine
Started	126	126
Completed	126	126

Period 2

Period 2 title	Completed
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

As before

Arms

Are arms mutually exclusive?	No
Arm title	Radiotherapy

Arm description:

Twenty gray (Gy) of radiation was administered to the retrobulbar orbit in 10-12 fractions over 2 to 3 weeks. Subjects receiving sham radiotherapy also attended and underwent all the same procedures other than no radiation being delivered.

Arm type	Factorial intervention
Investigational medicinal product name	Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor
Routes of administration	Route of administration not applicable

Dosage and administration details:

Twenty gray (Gy) of radiation was administered to the retrobulbar orbit in 10-12 fractions over 2 to 3 weeks.

Arm title	Azathioprine

Arm description:

Treatment dose varied between 100mg and 200mg daily (dispensed as 50 mg tablets), depending on body weight. Matched placebo tablets and packaging were used and the dose was adjusted according to a standard algorithm dependent on patient’s blood test results. Again, extensive effort was taken to ensure participants were unaware if they were receiving placebo, including identical blood tests and random placebo dose adjustments. To reduce the risk of serious adverse events, patients with abnormal

TPMT activity who are at increased risk of developing bone marrow suppression (low activity) or hepatotoxicity (high activity) with azathioprine were not enrolled.

Arm type	Factorial intervention
Investigational medicinal product name	Azathioprine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment dose varied between 100mg and 200mg daily (dispensed as 50 mg tablets), depending on body weight. Matched placebo tablets and packaging were used and the dose was adjusted according to a standard algorithm dependent on patient's blood test results. Again, extensive effort was taken to ensure participants were unaware if they were receiving placebo, including identical blood tests and random placebo dose adjustments. To reduce the risk of serious adverse events, patients with abnormal TPMT activity who are at increased risk of developing bone marrow suppression (low activity) or hepatotoxicity (high activity) with azathioprine were not enrolled.

Number of subjects in period 2	Radiotherapy	Azathioprine
Started	126	126
Completed	103	103
Not completed	23	23
Protocol deviation	23	23

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	126	126	
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)	113	113	
From 65-84 years	13	13	
85 years and over	0	0	
Age continuous			
49.2 (SD 11.0)			
Units: years			
arithmetic mean	42.9		
standard deviation	± 11.0	-	
Gender categorical Units: Subjects			
Female	93	93	
Male	33	33	

End points

End points reporting groups

Reporting group title	Radiotherapy

Reporting group description:

Twenty gray (Gy) of radiation was administered to the retrobulbar orbit in 10-12 fractions over 2 to 3 weeks. Subjects receiving sham radiotherapy also attended and underwent all the same procedures other than no radiation being delivered.

Reporting group title	Azathioprine

Reporting group description:

Treatment dose varied between 100mg and 200mg daily (dispensed as 50 mg tablets), depending on body weight. Matched placebo tablets and packaging were used and the dose was adjusted according to a standard algorithm dependent on patient's blood test results. Again, extensive effort was taken to ensure participants were unaware if they were receiving placebo, including identical blood tests and random placebo dose adjustments. To reduce the risk of serious adverse events, patients with abnormal TPMT activity who are at increased risk of developing bone marrow suppression (low activity) or hepatotoxicity (high activity) with azathioprine were not enrolled.

Reporting group title	Radiotherapy

Reporting group description:

Twenty gray (Gy) of radiation was administered to the retrobulbar orbit in 10-12 fractions over 2 to 3 weeks. Subjects receiving sham radiotherapy also attended and underwent all the same procedures other than no radiation being delivered.

Reporting group title	Azathioprine

Reporting group description:

Treatment dose varied between 100mg and 200mg daily (dispensed as 50 mg tablets), depending on body weight. Matched placebo tablets and packaging were used and the dose was adjusted according to a standard algorithm dependent on patient's blood test results. Again, extensive effort was taken to ensure participants were unaware if they were receiving placebo, including identical blood tests and random placebo dose adjustments. To reduce the risk of serious adverse events, patients with abnormal TPMT activity who are at increased risk of developing bone marrow suppression (low activity) or hepatotoxicity (high activity) with azathioprine were not enrolled.

Primary: Binary Clinical composite outcome measure

End point title	Binary Clinical composite outcome measure

End point description:

Major criteria*
• Improvement of ≥1 grade in diplopia score
• Improvement of >8° of eye movement in any direction
• Reduction of ≥2 mm in proptosis
Minor criteria*
• Reduction of ≥2 mm in lid aperture
• Improvement of ≥1 grade in soft tissue involvement
• Improvement in best-corrected visual acuity of ≥1 line on the Snellen chart
• Patient-judged subjective improvement
Calculation of response
• Improved: improvement in ≥1 major criteria or ≥2 minor criteria
• No change: improvement or deterioration in ≤1 minor criterion
• Worse: deterioration in ≥1 major or ≥2 minor criteria (even if other criteria improve)
*All items refer to the worst eye.

End point type	Primary

End point timeframe:

48 weeks

End point values	Radiotherapy	Azathioprine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	123		
Units: 0 1				
number (not applicable)	123	123		

Attachments (see zip file)	BCCOM ITT APP/Fig 4A.pdf

Statistical analyses

Statistical analysis title	Logistic regression

Statistical analysis description:

Note it was a factorial analysis so all on azathioprine vs those who did not receive azathioprine and radiotherapy was done in a similar fashion

Comparison groups	Azathioprine v Radiotherapy
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.054
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	6.66
Variability estimate	Standard deviation

Notes:

[1] - For Azathioprine

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the trial so data is up to 48 weeks.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Radiotherapy
Reporting group description:	
Twenty gray (Gy) of radiation was administered to the retrobulbar orbit in 10-12 fractions over 2 to 3 weeks. Subjects receiving sham radiotherapy also attended and underwent all the same procedures other than no radiation being delivered.	
Reporting group title	Azathioprine
Reporting group description:	
Treatment dose varied between 100mg and 200mg daily (dispensed as 50 mg tablets), depending on body weight. Matched placebo tablets and packaging were used and the dose was adjusted according to a standard algorithm dependent on patient's blood test results. Again, extensive effort was taken to ensure participants were unaware if they were receiving placebo, including identical blood tests and random placebo dose adjustments. To reduce the risk of serious adverse events, patients with abnormal TPMT activity who are at increased risk of developing bone marrow suppression (low activity) or hepatotoxicity (high activity) with azathioprine were not enrolled.	

Serious adverse events	Radiotherapy	Azathioprine	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Endocrine disorders			
Any			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Radiotherapy	Azathioprine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 63 (77.78%)	46 / 62 (74.19%)	
Blood and lymphatic system disorders			

ANY subjects affected / exposed occurrences (all)	49 / 63 (77.78%) 115	46 / 62 (74.19%) 118	

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

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

There is some complexity to analysis in comparing the outcomes be it APP or ITT.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29396245