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1 Combined immunosuppression & radiotherapy in thyroid eye disease (CIRTED): a multi-
2 centre, factorial randomised controlled trial

3

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51

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53 **Abstract**

54 *Background*

55 Thyroid eye disease is a disabling inflammatory orbital condition which causes visual
56 dysfunction and psychological morbidity. Standard treatment is with systemic corticosteroids,
57 but the additional benefit of orbital radiotherapy and antiproliferative immunosuppression is
58 unclear.

59
60 *Methods*

61 Participants all received a 24 week course of oral prednisolone and were also randomised to
62 receive radiotherapy or sham-radiotherapy, and azathioprine or placebo, in a 2x2 factorial
63 design. The primary outcomes were a binary composite clinical outcome score and
64 ophthalmopathy index at 48 weeks and clinical activity score at 12 weeks. (ISRCTN
65 22471573).

66
67 *Findings*

68 126 adults with active moderate-to-severe thyroid eye disease were randomised. 103
69 provided outcome data, of which 84 completed their allocated treatment of radiotherapy or
70 sham-radiotherapy, and 57 continued to take azathioprine or placebo until 48 weeks. Pre-
71 specified intention-to-treat analysis of the binary clinical composite outcome measure
72 revealed an odds of improvement for azathioprine of $OR_{(adj)}=2.56$ (95%CI 0.98, 6.66;
73 $p=0.05$) and for radiotherapy of $OR_{(adj)}=0.89$ (95%CI 0.36, 2.23; $p=0.80$). In a post-hoc
74 analysis of patients completing their allocated therapy, improvement was more frequent on
75 azathioprine ($OR_{(adj)}=6.83$; 95%CI 1.66, 28.1; $p=0.008$) than radiotherapy ($OR_{(adj)}=0.71$;
76 95%CI 0.26, 1.95; $p=0.50$). The ophthalmopathy index, clinical activity score and number
77 of adverse events (azathioprine N=161, radiotherapy N=156) did not differ between treatment
78 groups.

79
80 *Interpretation*

81 In patients receiving oral prednisolone for 24 weeks, the addition of radiotherapy was not
82 beneficial. With regard to azathioprine, our conclusions are limited by a high number of
83 withdrawals from treatment. However, these results suggest that disease severity at 48 weeks
84 was reduced in participants who completed azathioprine treatment.

85
86 *Funding*

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88 *infrastructural investment from the National Institute for Health Research*

89

90

Research in Context

Active moderate-to-severe thyroid eye disease is currently treated with systemic corticosteroids, but outcomes are often sub-optimal. Corticosteroids are most effective when administered intravenously, but this is inconvenient, and oral administration remains common in global clinical practice. However, uncertainty remains about the additional benefit of orbital radiotherapy and antiproliferative immunosuppressive drugs.

Evidence before this study

Previous retrospective case series have reported that the antiproliferative immunosuppressive drug azathioprine reduces disease severity and the need for rehabilitative surgery, but no prior RCTs have been completed. The evidence base for orbital radiotherapy is stronger, but conflicting, especially in the context of systemic corticosteroid treatment.

Added value of this study

Eighty per cent of subjects completed radiotherapy, but no significant short (12 week) or long-term (48 week) benefit resulted over and above the improvement seen with a 24-week tapering course of oral corticosteroids. Less strong conclusions can be drawn with regard to azathioprine, as many patients did not complete treatment due to abnormalities in monitoring blood tests or side-effects, but those that continued azathioprine for more than 24 weeks benefitted, predominantly due to a prevention of deterioration after the end of corticosteroid treatment.

Implications of all the available evidence

These results do not support the use of radiotherapy in thyroid eye disease in patients also treated with systemic corticosteroids. They also provide evidence in favour of the use of anti-proliferative immunosuppressive agents such as azathioprine beyond the period of corticosteroid therapy to improve long-term clinical outcomes.

92 **Introduction**

93 Active moderate-to-severe thyroid eye disease, also known as Graves' orbitopathy or thyroid
94 associated orbitopathy) occurs in 5-10% of cases of Graves' disease(1). It can be both
95 visually disabling and cosmetically disfiguring and substantially impairs quality of life(1-3).
96 The aim of treatment is to suppress orbital inflammation and reduce consequent tissue re-
97 modelling in extraocular muscles, orbital fat and other periocular soft tissues(4, 5).
98 Immunosuppressive therapies, in particular corticosteroids(1, 4, 6), are the mainstay of
99 treatment for active moderate-to-severe thyroid eye disease (1). However, they are typically
100 withdrawn after 24 weeks of treatment to limit cumulative toxicity regardless of whether they
101 are administered via the oral or intravenous route(7), and given that active disease lasts 1–2
102 years, recurrence at the time of withdrawal often occurs(1, 7-9).

103

104 Consequently, the avoidance of corticosteroid side-effects, improvement in treatment efficacy
105 and maintenance of long-term disease control are major goals for the field of thyroid eye
106 disease as a whole. However, efforts to use monoclonal antibody therapies to more
107 selectively suppress disease are still either early in their route to market(10), or have failed to
108 demonstrate definitive treatment benefit(11, 12). Hence, given the proven short-term efficacy
109 of corticosteroids in the treatment of active moderate-to-severe thyroid eye disease, it is
110 likely that they will remain the gold-standard first-line treatment for several years to come,
111 and the need to find adjunctive therapies to augment and sustain their benefit remains very
112 real.

113

114 To date, the only non-corticosteroid conventional immunosuppressant drug to have been
115 evaluated in RCTs is cyclosporine A(13, 14), which was found to be beneficial, but its use
116 has not been widely adopted because of concerns about side-effects(6). An alternative
117 strategy is to use an antiproliferative agent such as azathioprine as it is better tolerated than
118 cyclosporine A(15, 16) and although ineffective as monotherapy(17), retrospective data
119 indicates that in combination with corticosteroids it reduces disease severity and the need for
120 rehabilitative surgery(18). In addition to immunosuppression, non-pharmaceutical treatment

121 of active thyroid eye disease with orbital radiotherapy has been advocated for decades, and
122 older RCTs demonstrated that this was more effective when used in combination with
123 corticosteroids(19, 20). However, subsequent studies either questioned the role of orbital
124 radiotherapy or concluded that its benefit was limited to improvement in oculomotility(21-
125 23). This has generated significant controversy, in particular due to concerns about the entry
126 criteria, trial design and radiotherapy administration in Gorman et al's paper(22), which has
127 led to disparity in practice. Orbital radiotherapy has now been largely abandoned in North
128 America, whereas in European centres, including the UK, it is still routinely used(6, 23-25).
129 As it is administered daily over 2-3 weeks and patients are typically of working age, this also
130 has significant implications for the use of healthcare resources and patients' time.
131 Furthermore, only two relatively small studies have evaluated the additional effect of
132 radiotherapy when combined with a high-dose course of systemic corticosteroids(19, 20), and
133 clinical outcomes beyond 24 weeks have rarely been reported for any intervention in thyroid
134 eye disease. We therefore sought to evaluate the long-term benefit of orbital radiotherapy and
135 antiproliferative immunosuppression with azathioprine in the context of sustained systemic
136 corticosteroid treatment for active moderate-to-severe thyroid eye disease .

137

138 **Methods**

139 *Study design and participants*

140 We undertook this factorial design multicentre RCT in 6 centres in the UK. Patients aged 20-
141 75 years were recruited to receive either azathioprine or placebo, *plus* either orbital
142 radiotherapy or sham-radiotherapy, in *combination* with a standardised 24-week tapering oral
143 prednisolone regime (**Supplementary Table 1 and Supplementary Figure 1**). In brief, all
144 patients received an initial oral prednisolone dose of 80mg / day, which reduced to 20mg /
145 day by 6 weeks, 10mg / day by 15 weeks and 5mg / day by 21 weeks. In accordance with the
146 factorial design, study recruits were then randomly allocated into 4 groups 2 weeks after
147 starting corticosteroids: azathioprine plus orbital radiotherapy, azathioprine plus sham-
148 radiotherapy, placebo plus orbital radiotherapy, or placebo plus sham-radiotherapy. Full
149 protocol details, including pre-specified primary and secondary outcome measures and

150 statistical analyses, have been previously peer-reviewed, published and are openly
151 available(26). Trial registration was assigned retrospectively on 1 February 2006
152 (ISRCTN22471573) following regulatory permissions, but prior to starting recruitment.

153

154 Eligible patients had a clinical activity score(27) ≥ 4 (worst eye) OR ≥ 2 (worst eye) with a
155 history of proptosis or motility restriction of less than 6 months duration. They were also
156 required to have a past or present history of abnormal thyroid function or a clinical diagnosis
157 of thyroid eye disease made and confirmed by ≥ 2 muscle involvement on computed
158 tomography or magnetic resonance imaging scan. The clinical activity score was scored out
159 of 7 at the enrolment visit as its last 3 items (decreasing proptosis, decreasing visual acuity
160 and decreasing eye movement) require a change in consecutive measurements to be
161 calculated. This therefore cannot be done at the first assessment, but at all subsequent visits
162 clinical activity score was scored out of 10. If study recruits *either* had a < 6 month history
163 of thyroid eye disease (defined as time since first symptom) *or* an improvement in any item
164 of clinical activity score 2 weeks after starting the trial prednisolone regime, they were
165 considered to have active disease and were randomised at the second trial visit. Key
166 exclusion criteria included age < 20 or > 75 years, dysthyroid optic neuropathy, abnormal
167 thiopurine methyltransferase activity and use of radioiodine or any immunomodulatory or
168 cytotoxic drugs within the last 3 months (thyroidectomy was permitted).

169

170 *Randomisation and masking*

171 Patients' eligibility for the study was assessed by the ophthalmic investigators at each trial
172 centre. Allocation to treatment groups was by remote computerised randomisation and
173 minimisation was used to reduce baseline disparities in potential confounding variables
174 between trial interventions. These included smoking status at the time of thyroid eye disease
175 diagnosis, thyroid status on enrolment, previous corticosteroid use, gender, disease
176 severity, study centre, disease duration, age greater than 60 years and disease
177 activity. Patients, clinicians (both ophthalmic and endocrine) and data analysts were all
178 masked. Only the trial co-ordinators (who monitored trial subjects blood results), pharmacists

179 and radiographers were unmasked. The success of masking for ophthalmic investigators and
180 patients was assessed at study completion or withdrawal by asking them to declare which
181 treatments they thought had been administered.

182

183 *Procedures*

184 *Orbital radiotherapy*

185 Twenty gray (Gy) of radiation was administered to the retrobulbar orbit in 10-12 fractions
186 over 2 to 3 weeks. Subjects receiving sham-radiotherapy also attended and underwent all the
187 same procedures other than no radiation being delivered. Extensive effort was used across
188 trial centres to ensure participants were unable to identify if they were receiving sham
189 therapy, including use of a noise emitting device to simulate treatment administration(26) (for
190 details of the radiotherapy procedures at each trial centre see **Supplementary Text 2**)

191

192 *Azathioprine*

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

201

202 *Follow-up and withdrawals*

203 Follow-up continued for a minimum of 48 weeks. Withdrawn subjects were returned to their
204 referring ophthalmologist, however they were invited to attend assessment visits at the early
205 (co-primary) and late (primary) outcome measure assessment times of 12 and 48 weeks to
206 obtain data in accordance with the planned intention-to-treat analyses. Withdrawal criteria
207 included worsening of disease (defined as a 2-point increase in clinical activity score or

208 development of optic neuropathy) and sustained blood test abnormalities (leucopenia,
209 lymphopenia or abnormal liver function tests despite dose adjustment of azathioprine or
210 placebo).

211

212 *Ethical approval and Trial Oversight*

213 The trial protocol was given a favourable opinion by the UK's National Health Service South
214 West Central Bristol Research Ethics Committee (REC reference: 05/Q2006/62). Clinical
215 Trial Authorisation was given by the Medicines and Healthcare products Regulatory Agency
216 (MHRA, reference: 03299/0003/001-0001; ISRCTN22471573) with the University of Bristol
217 acting as the legal sponsor. Research governance and local Research and Development
218 approvals were obtained across all sites prior to the start of recruitment. All participants gave
219 written informed consent, and the conduct of the trial was subject to independent Data Safety
220 Monitoring Committee and Trial Steering Committee review for the duration of the study.

221

222 *Outcomes*

223 As the principle objective of the trial was to evaluate treatment success and failure at the late
224 time-point of 48 weeks, our primary outcome measures of disease severity binary clinical
225 composite outcome measure (**BOX 1**) and Ophthalmopathy Index (**Supplementary Table 2**)
226 were selected to quantify the change in ocular deformity and visual dysfunction. An early,
227 12-week, assessment of disease activity using the clinical activity score was given lower
228 priority and designated as a co-primary outcome (we expected that all participants would
229 have a significant improvement in clinical activity score by 48 weeks in accordance with the
230 natural history of the disease(28)). Secondary outcome measures included Total Eye Score

Box 1 Calculation of the Binary Clinical Composite Outcome Measure

Major Criteria

- An improvement of ≥ 1 grade in diplopia score
- An improvement of >8 degrees of eye movement in any direction
- A reduction of ≥ 2 mm in proptosis

Minor Criteria

- A reduction of ≥ 2 mm in lid aperture
- 9 ▪ An improvement of ≥ 1 grade in soft tissue involvement
- An improvement in best-corrected visual acuity of ≥ 1 line on the Snellen chart
- Subjective improvement

All items refer to the worst eye

Response to treatment is calculated as follows

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)

231 **(Supplementary Table 3)** as an additional assessment of disease severity, patient-reported
232 Graves' Ophthalmopathy Quality of Life score and health economic indices.

233

234 *Statistical analyses*

235 Planned statistical analyses were pre-specified in our protocol paper, based on a sample size
236 of 100 complete datasets at 48 weeks(26). These were undertaken according to CONSORT
237 guidelines for RCTs. As required by the factorial design, the primary intention-to-treat
238 analysis (ITT) combined the treatment groups to compare radiotherapy versus sham-
239 radiotherapy and azathioprine versus placebo for each of the two primary outcomes at 48
240 weeks follow up. This analysis was made using multivariable regression models, adjusting
241 for minimisation variables, the factorial design, and the value of the outcome variable at
242 baseline. Statistical significance was defined in advance as a p-value of <0.05. Patients who
243 had no outcome data for the primary analyses had data imputed using last observation carried
244 forward if they had data available between 24-48 weeks. Analysis was performed for all
245 primary outcomes (binary clinical composite outcome, ophthalmopathy index and clinical
246 activity score). Patients who withdrew from treatment due to side-effects, disease
247 progression or personal preference, were encouraged to continue to attend for follow-up
248 assessments and their data included in the intention-to-treat analyses. Since there were a large
249 number of withdrawals from treatment (although most trial subjects still returned for
250 assessment at the primary endpoint visit), a post-hoc as-per-protocol analysis was conducted
251 including only patients who had not withdrawn and continued to receive their assigned
252 treatment. Testing for interaction was performed using likelihood ratio tests. Additional
253 sensitivity analyses were performed for the binary clinical composite outcome measure,
254 including recoding those who withdrew due to deterioration, irrespective of their final status
255 at 48 weeks (as they may have received alternative rescue therapy). The secondary outcome
256 measures of Total Eye Score and Graves ophthalmopathy quality-of-life score were also
257 compared across treatment groups, however patient-reported health economic analyses were
258 not completed due to insufficient data. All statistical analyses were undertaken using
259 STATA version 12 (STACORP, College Station, TX, USA).

260 *Study Sponsor and role of the funding source*

261 The study sponsor was the University of Bristol. Funding was provided by the UK's National
262 Eye Research Centre, Above and Beyond and Moorfields Eye Charity supported by
263 infrastructural investment from the National Institute for Health Research. The sponsor and
264 funders had no role in the study design, in the collection, analysis, and interpretation of data,
265 in the writing of the report or in the decision to submit the paper for publication. In addition,
266 the corresponding author had full access to all of the data and the final responsibility to
267 submit for publication (PNT RH CMD and RL had access to the raw data).

268

269 **Results**

270 *Study Population*

271 126 people were recruited and randomised between February 2006 and October 2013 (71
272 patients from Moorfields Eye Hospital, 34 from Bristol Eye Hospital, 7 from Manchester Eye
273 Hospital, 5 from the Western Eye Hospital, 4 from University College London Hospital, 4
274 from Gartnavel General Hospital and 1 from the University Hospital of Wales). The flow of
275 study participants is shown in **Figure 1**. Data on both the primary outcomes at 48 weeks was
276 provided by 103 participants, and these were analysed after data-lock (which included
277 separate 3 year assessments on a minority of trial subjects) on 7th October 2016. Baseline
278 characteristics of the minimisation variables by group are shown in **Table 1**. Individuals
279 allocated to azathioprine had a relatively lower proportion of non-Caucasian patients (not a
280 criterion used for minimisation).

281

282 *Intention-to-treat analysis*

283 *Binary Clinical Composite Outcome Measure (primary outcome)*

284 The difference in the binary clinical composite outcome measure between individuals
285 randomised to azathioprine versus placebo tablets was on the threshold of our pre-specified
286 significant p-value of <0.05, but did not meet this (the adjusted OR_(adj) of the binary clinical
287 composite outcome measure's improvement on azathioprine was 2.56; 95%CI 0.98, 6.66;
288 p=0.05, **Table 2 Figure 2A**). In contrast, there was no improvement with orbital radiotherapy

289 (OR_(adj) =0.89, 95%CI 0.36, 2.23, p=0.80). Also, with regard to the factorial design, there
290 was no evidence of interaction between azathioprine and radiotherapy (p_{int} = 0.86) and the
291 combination of azathioprine and orbital radiotherapy did not offer additional advantage over
292 azathioprine alone. An overview of the impact on the binary clinical composite outcome
293 measure of azathioprine and orbital radiotherapy is shown in **Supplementary Figure**
294 **2A+2B**. Furthermore, additional sensitivity analyses in which withdrawn patients were coded
295 to unfavourable outcomes regardless of their status at 48 weeks enhanced rather than lessened
296 the improvement observed with azathioprine treatment (OR_(adj) 3.65; 95%CI 1.34, 9.86;
297 p=0.01) (**Supplementary Table 4**).

298

299 *Ophthalmopathy Index (primary outcome)*

300 Analysis of all patients revealed that the ophthalmopathy index fell between week 12 (mean
301 9.15, SD 0.39) and week 48 (mean 8.43, SD 0.38, p=0.04). No additional benefits were seen
302 with either azathioprine or orbital radiotherapy. Individuals randomised to azathioprine had
303 an adjusted Beta (B)_(adj) of 0.46 (95%CI -1.04, 1.95; p=0.55) and in those randomised to
304 orbital radiotherapy B_(adj) was -0.89 (95%CI -2.34, 0.56; p=0.23) (**Table 2**). There was also
305 no evidence of an interaction between azathioprine and radiotherapy in their effect on
306 ophthalmopathy index (p_{int} = 0.51).

307

308 *Clinical Activity Score (co-primary outcome)*

309 Across all subjects, substantial improvement in median clinical activity score was seen over
310 the study period from 5 (IQR 4 - 5) at baseline to 3 (IQR 2- 4; p<0.0001) at week 12, and 2
311 (IQR 1-3; p<0.0001) at week 48 (**Figure 2B, 2C**). The majority of patients n=97 (70.0%)
312 improved their clinical activity score by week 12 and 96 (98%) of the 98 patients with
313 clinical activity score data at 48 weeks showed improvement in their clinical activity score
314 versus baseline. No difference in the change in clinical activity score at 12 weeks was
315 observed between individuals who received treatment with azathioprine versus not receiving
316 azathioprine, or who received radiotherapy versus sham radiotherapy B_(adj)= -0.01 (95%CI -
317 0.69, 0.68; p=0.99 – **Table 2**). There was no interaction between azathioprine and

318 radiotherapy in their effect on clinical activity score ($p_{\text{int}}= 0.48$). There was also no evidence
319 that azathioprine or orbital radiotherapy improved clinical activity score at week 48
320 (**Supplementary Table 5**).

321

322 *Total Eye Score (secondary outcome)*

323 Total Eye Score improved considerably over the study period with a mean at baseline of 15.1
324 (95%CI 13.8, 16.3) falling to a mean of 9.36 (95%CI 8.12, 10.6; $p < 0.0001$), but this was
325 not affected by the addition of either azathioprine or orbital radiotherapy (**Supplementary**
326 **Table 6**).

327

328 *Graves Ophthalmopathy Quality of Life (secondary outcome)*

329 Across all subjects, mean Graves ophthalmopathy quality of life visual function was higher
330 (improved) at 12 weeks than at baseline (71.5 - 95%CI 66.1, 76.9 vs 64.1 - 95%CI 58.5,
331 70.0; $p=0.002$), and at week 48 (75.5 - 95%CI 70.3, 80.7; $p<0.001$ versus baseline). Graves
332 ophthalmopathy quality of life visual appearance was also higher at 12 weeks than at baseline
333 (58.0 - 95%CI 52.5, 63.5 vs 53.2 - 95%CI 47.9, 58.6; $p=0.007$) and at week 48 (61.3 -
334 95%CI 55.6, 67.1; $p=0.001$ versus baseline). Individuals who had an improvement in the
335 binary clinical composite measure at week 48 had a higher Graves ophthalmopathy quality of
336 life visual function ($B=17.9$ - 95%CI 7.07, 28.6; $p<0.001$) and a higher Graves
337 ophthalmopathy quality of life visual appearance ($B_{\text{(adj)}}=11.5$ - 95%CI 0.60, 23.6; $p=0.06$).
338 There was no clear benefit from the addition of either azathioprine or orbital radiotherapy
339 with regard to long-term Graves ophthalmopathy quality of life visual function or visual
340 appearance (**Supplementary Table 7, Supplementary Figure 3**).

341

342 *As-per-protocol analysis*

343 Sixty individuals did not withdraw from study treatment before 48 weeks, completed their
344 therapy period as allocated and were included in the as-per-protocol analysis. Ten of these
345 patients were randomised to azathioprine and sham-radiotherapy, 17 were randomised to
346 orbital radiotherapy and placebo alone, 12 were randomised to azathioprine and orbital

347 radiotherapy and 21 were randomised to sham-radiotherapy and placebo. Individuals in the
348 as-per-protocol analysis appeared similar at baseline to those who were withdrawn from
349 study treatment, although there was a higher percentage of non-Caucasians in those recruited
350 from the larger study centres (**Supplementary Table 8**).

351

352 In the as-per-protocol analysis, individuals randomised to receive azathioprine (n=22) had a
353 higher odds ratio of improvement in their disease severity measured by the primary binary
354 clinical composite outcome measure at 48 weeks ($OR_{(adj)}=6.83$, 95%CI 1.66, 28.1; $p=0.008$).
355 No benefit was seen in individuals randomised to receive orbital radiotherapy ($OR_{(adj)} 1.32$,
356 95%CI 0.36, 4.84; $p=0.67$, **Table 3 Figure 2A**). To assess the effect of the duration of
357 exposure to azathioprine we also conducted a comparative analysis of patients who continued
358 to receive their allocated treatments at 12 weeks (n=84), 24 weeks (n= 79) and 36 weeks
359 (n=68). This indicated that benefit was observed with ≥ 24 weeks of azathioprine exposure
360 (**Figure 2A, Supplementary Table 9 and Supplementary Figure 2A**). Individuals
361 receiving azathioprine also had a modest improvement in total eye score ($B_{(adj)}= -3.23$,
362 95%CI -6.42, 0.03; $p=0.05$, **Supplementary Table 6**). However, the as-per-protocol analysis
363 did not reveal any benefit in ophthalmopathy index, clinical activity score or Graves
364 ophthalmopathy quality of life of being randomised to receive either azathioprine or orbital
365 radiotherapy (**Table 3**).

366

367 *Withdrawals from the study*

368 There was a high number of patients who withdrew from their allocated treatment (n=66,
369 52.4%) (**Figure 1**), but the majority of these (n=45, 68.2%) returned for primary outcome
370 evaluation. Twenty-five withdrawals were within the first 12 weeks (**Figure 3**). Withdrawals
371 were less in non-Caucasians and in participants at two of the study centres (Moorfields and
372 Bristol Eye Hospitals). Before 48 weeks there were 40 withdrawals in those randomised to
373 receive azathioprine and 34 withdrawals in those randomised to receive orbital radiotherapy.
374 Overall, 103 participants provided outcome data, of which 84 completed their allocated
375 treatment of radiotherapy or sham-radiotherapy, and 57 continued to take azathioprine or

376 placebo until 48 weeks. Participants randomised to receive azathioprine had increased odds
377 of withdrawal compared to those who did not $OR_{(adj)}=2.82$ (95%CI 1.23, 6.45) $p=0.01$
378 (**Supplementary Table 10**). The reasons for withdrawal are presented in **Supplementary**
379 **Figure 4**. Patients receiving azathioprine had an increased odds of withdrawal due to
380 precautionary blood test abnormalities or side effects $OR=9.10$ (95%CI 2.60, 31.9) $p=0.001$
381 (**Supplementary Table 11**). However, unlike patients receiving placebo, patients taking
382 azathioprine did not withdraw due to deterioration following cessation of steroid treatment at
383 24 weeks (**Figure 3C**). No baseline characteristics predicted withdrawal due to either
384 azathioprine or orbital radiotherapy although the highest odds of withdrawal for disease
385 deterioration was in the sham-radiotherapy and placebo group (**Supplementary Table 12**).
386 There was no evidence of bias between treatment groups with regard to failure to provide
387 data at 48 weeks (**Supplementary Table 13** and **Supplementary Table 14**).
388

389 *Rescue therapy (including surgery) and adverse events*

390 Twenty-one (47%) of the trial subjects who withdrew from study treatment but provided
391 outcome data were documented to have received additional therapy (**Supplementary Table**
392 **15**). In most cases this was additional steroid therapy continuing until the endpoint of the
393 study (week 48). Surgery was however required in 5 individuals, 3 of whom were in the
394 azathioprine group (3 orbital decompressions, 1 lid surgery and 1 strabismus correction). The
395 number of individuals experiencing an adverse event did not differ across the treatment
396 groups (azathioprine $N=161$, radiotherapy $N=156$). (**Supplementary Table 16** and
397 **Supplementary Table 17**).
398

399 *Masking*

400 Of the 69 patients and 71 doctors who recorded their perceived trial allocation for
401 azathioprine or placebo on study completion or withdrawal, 30 patients (43%) and 29 doctors
402 (41%) were incorrect. For radiotherapy and sham-radiotherapy, of the 70 patients and 67
403 doctors, 23 patients (33%) and 33 doctors (49%) were incorrect.
404

405 **Discussion**

406 CIRTED fulfilled its target sample size, with more than 100 complete data sets at 48 weeks.
407 Improvement in our primary, co-primary and secondary outcome measures (binary clinical
408 composite outcome measure, clinical activity score and Graves ophthalmopathy quality-of-
409 life score) across all groups confirmed the previously reported benefits of high dose systemic
410 corticosteroid therapy in active moderate-to-severe thyroid eye disease (**Figures 2B and 2C**).
411 In this context, orbital radiotherapy did not confer additional patient benefit in any pre-
412 specified outcome measure either in the short (12-week) or longer term (48-week).
413 Radiotherapy was delivered early in the treatment (before 12 weeks); hence it is unlikely that
414 this result is significantly confounded by the high withdrawal rate later in the treatment
415 course.

416
417 Less strong conclusions can be drawn with regard to azathioprine as comparatively few
418 patients completed the full course of treatment. Nonetheless, the improvement in the binary
419 clinical composite outcome measure observed in the azathioprine-treated group of subjects
420 that was on the threshold of statistical significance in our intention-to-treat analysis ($p=0.05$)
421 is likely to be real as the effect was sustained or enhanced in our sensitivity analyses
422 (**Supplementary Table 4, Supplementary Table 9**). This is reinforced by the post-hoc as-
423 per-protocol analysis results which showed substantial benefit in favour of azathioprine
424 ($OR_{(adj)}=6.83$ $p=0.008$). Of note, patient outcomes improved particularly in those receiving
425 azathioprine for 24 weeks or more (figure 3A). Since steroid therapy was stopped at 24
426 weeks (as is common practice in thyroid eye disease), this suggests that the key benefit of
427 azathioprine is to prevent relapse after withdrawal of steroids. This observation is consistent
428 with the generally recognised role of azathioprine as a steroid-sparing agent, used to prevent
429 relapse in other autoimmune conditions, and this is further reinforced by the findings of the
430 MINGO study using an alternative antiproliferative agent (mycophenolate sodium) in thyroid
431 eye disease. Furthermore, this view is supported by analysis of the binary clinical composite
432 outcome measure components indicating that azathioprine did not increase major
433 improvement rates overall but did reduce major deterioration in the binary clinical composite

434 outcome measure ($p=0.004$, **Supplementary Figure 2A**), plus the observation that late
435 withdrawal (after 24 weeks) due to deterioration was not seen in patients treated with
436 azathioprine (**Figure 3C**).

437

438 A major feature of this study was the high rate of withdrawal from patients' allocated
439 treatment. In all study groups, early withdrawals (before 24 weeks) due to disease
440 deterioration were seen as the steroid dose was reduced and this was not mitigated by orbital
441 radiotherapy (**Figure 3C**). Our masked protocol necessarily set strict thresholds for
442 withdrawal due to abnormal monitoring blood tests (white cell counts and liver function),
443 which together with treatment side-effects led to more common withdrawals in those
444 allocated to azathioprine (**Figure 3B**). Hence, it is likely that in usual clinical practice
445 azathioprine treatment would be continued in a higher percentage of patients. Importantly,
446 many of those withdrawing from treatment still completed their study follow-up visits until
447 the primary endpoint (48 weeks), resulting in the outcomes for over 80% of randomised
448 subjects being available for our intention-to-treat analysis.

449

450 The other key methodological point to consider is our use of two primary outcome measures
451 at 48 weeks. As we have previously published (26), this was because of the lack of fully
452 validated long-term disease severity measures in thyroid eye disease. We also wished to
453 mitigate the theoretical limitations of composite binary scoring systems, in particular with
454 regard to baseline variability between treatment groups, by using a continuous variable with
455 regression analyses in mind. However, our minimisation strategy was successful in balancing
456 baseline features across trial arms and the binary clinical composite outcome measure has
457 since become the preferred end-point for thyroid eye disease studies as it is more sensitive to
458 change(21, 23). We have therefore focused on this rather than the ophthalmopathy index
459 which has not been a primary endpoint in other recent trials.

460

461 The key strengths of this RCT include the use of minimisation, low rates of loss-to-follow-up
462 (including of withdrawn patients) and the success of our extensive efforts to mask both

463 azathioprine and radiotherapy treatment allocation to both the patients and clinicians
464 (including the use of sham radiotherapy). In addition, we observed no evidence of interaction
465 between the two interventions (radiotherapy and azathioprine), which is supportive of our
466 choice of a factorial design. Conversely, a major limitation of our study was the high
467 withdrawal rate, particularly for those randomised to receive azathioprine. Therefore, our
468 conclusions with regard to the efficacy of this treatment need to be interpreted with caution.
469 We also permitted patients to enrol in the trial and start systemic corticosteroid therapy
470 before their thyroid function tests were normalised. This potentially confounds the
471 interpretation of our data with the benefit of returning to euthyroidism, but we judged
472 intervening with immunosuppression in the early active phase of disease to outweigh this
473 risk. Furthermore, given that demonstration of clinical improvement following a 2-week
474 course of high-dose oral steroids was a key entry criterion, our results cannot be extrapolated
475 to infer the value of radiotherapy or azathioprine in patients with steroid refractory disease.
476 Oral corticosteroid therapy was used in this study and given to all study participants as this
477 was the standard of care in the study centres at the time of trial initiation and remains
478 commonly prescribed in many regions of the world including North America (29).

479
480 In summary, our results suggest that low-dose orbital radiotherapy confers no additional short
481 or long-term treatment benefit when combined with a six-month reducing course of oral
482 corticosteroids. Our findings with regard to azathioprine are less definitive, but taken together
483 indicate that, if tolerated, azathioprine improves 48-week clinical outcomes in patients with
484 active moderate-to-severe thyroid eye disease. This supports the use of long-term
485 antiproliferative treatments in combination with systemic corticosteroids for the treatment of
486 active moderate-to-severe thyroid eye disease, consistent with established practice in other
487 autoimmune conditions.

488

489

490 **Table and figure headings**

491	Table 1	Characteristics of the 4 trial groups
492	Table 2	Intention to treat analysis Binary Composite Clinical Outcome Measure,
493		Ophthalmopathy Index and Change in Clinical Activity Score
494	Table 3	As per protocol analysis Binary Composite Clinical Outcome Measure,
495		Ophthalmopathy Index and Change in Clinical Activity Score
496		
497	Figure 1	Consort Diagram
498	Figure 2A	Odds ratio of having an improved Binary Composite Clinical Outcome
499		Measure score by treatment and duration in study
500	Figure 2B	Boxplot of Clinical Activity Score at baseline, week 12 and week 48 by
501		whether a participant was randomised to azathioprine
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503		whether a participant was randomised to radiotherapy
504	Figure 3A	Kaplan Meier survival showing withdrawals from treatment (all reasons)
505	Figure 3B	Kaplan Meier survival showing withdrawals from treatment (side effects and
506		abnormal blood results)
507	Figure 3C	Kaplan Meier survival showing withdrawals from treatment (deterioration)
508		

509

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549

550 **Declaration of Interest**

551 The authors report no declarations of interest

552

553 **References**

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