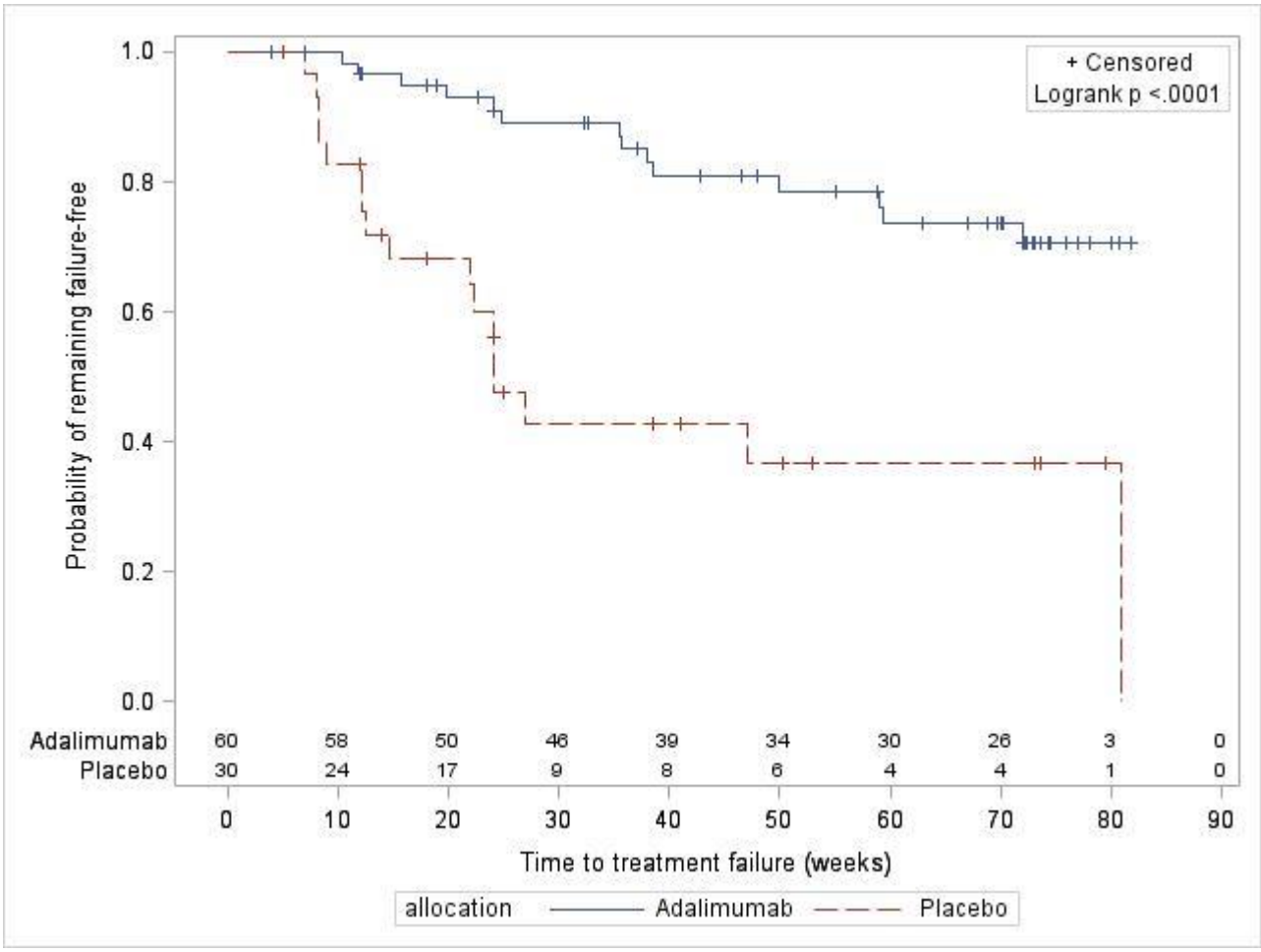
Blinded phase: Time to treatment failure

Figure 1 shows the Kaplan-Meier plot for time to treatment failure in the blinded phase.

Figure 1: Primary outcome ITT Kaplan-Meier plot



Sensitivity Analyses

The nine sensitivity analyses that were conducted are listed below:

- Best-case: All participants that withdrew from treatment were treated as censored at time of treatment withdrawal.

- Worst case: All participants that withdrew from treatment were treated as treatment failures i.e. events at time of treatment withdrawal.

- Methotrexate: Any participants that withdrew from treatment due to methotrexate intolerance were classified as treatment failures at the time of treatment withdrawal.

- Component 1 of primary outcome: All patients that failed for component 1 at a treatment failure assessment had their event date as the mid-point between this visit and previous visit instead of the date of this visit.

- Component 2 of primary outcome: All patients that failed for component 2 at a treatment failure assessment had their event date as the date that they commenced on the concomitant medications (i) used against pre-defined acceptable criteria (see SYCAMORE trial protocol (49)), or (ii) any of the concomitant medications not allowed. The event date was determined by the Co-Chief Investigators making a clinical decision following review of the patients' concomitant medications taken since their previous visit.

- Component 3: All patients that failed for component 3 at a treatment failure assessment had their event date as the exact date that they qualified as 'Intermittent or continuous suspension of study treatment (adalimumab/placebo) for a cumulative period longer than 4 weeks'. The event date was determined by the Chief Investigator making a clinical decision following review of the patients' trial treatment dose recordings in the treatment diaries.

- Any missing primary outcome data: Any cases of missing data for any of the primary outcome components (except for unscheduled visits) had data imputed on a worst-case basis due to the fact that the missing data could have meant that a participant failed earlier than recorded. All patients were treated the same regardless of whether they have had a treatment failure or not.

- Loss to follow-up: In the primary analysis of primary outcome, patients that were lost to follow-up were treated as withdrawals assuming that they were non-informative. The reasons for loss to follow-up, where available, were blindly reviewed by Professor Michael William Beresford (Co-Chief Investigator) and Professor Andrew Dick (Ophthalmology expert on TMG) to see whether they thought any might be related to prognosis. If any were deemed to be related, a sensitivity analysis would be undertaken assuming these patients to be a treatment failure at the time of last recorded visit.

- Incorrectly identified to be a treatment failure: Once a patient had been deemed to have had failed treatment, treatment was stopped and they entered the follow-up phase of the study providing they still wish to be followed up. If there were any patients that were wrongly identified to be treatment failures by the assessing physician they would be classed as a withdrawal at their time of 'treatment failure'.

The results of the nine sensitivity analyses can be seen in Table 1, which contains information on the number analysed in each group, the number of treatment failures, the number of participants censored, the log-rank chi-square statistic, the log-rank p-value, the HR and the 95% CI.

There were no losses to follow-up and no incorrect treatment failures, therefore, sensitivity analysis eight and nine were not conducted. The results of the other sensitivity analyses indicate that the original conclusion from the primary analysis was robust with regards to the assumptions that were made. The overall statistical significance in the sensitivity analyses did not change.

Table 1: Primary outcome ITT analysis and sensitivity analyses results

Analysis	N	Adalimumab			Placebo			Log-rank chi-square statistic	Log-rank p-value	HR	(95% CI)
		n	Treatment failures	Censored	n	Treatment failures	Censored				
ITT	90	60	14	46	30	17	13	16.72	<0.0001	0.25	(0.12, 0.51)
Sens (1) – best case	90	60	13	47	30	15	15	19.98	<0.0001	0.21	(0.10, 0.44)
Sens (2) – worst case	90	60	24	36	30	23	7	24.17	<0.0001	0.25	(0.14, 0.46)
Sens (3) – MTX	90	60	19	41	30	17	13	10.45	0.001	0.34	(0.18, 0.68)
Sens (4) – Component 1	90	60	14	46	30	17	13	17.67	<0.0001	0.24	(0.12, 0.49)
Sens (5) – Component 2	90	60	14	46	30	17	13	16.93	<0.0001	0.24	(0.12, 0.50)
Sens (6) – Component 3	90	60	14	46	30	17	13	16.77	<0.0001	0.25	(0.12, 0.51)
Sens (7) – Missing PO	90	60	14	46	30	17	13	16.72	<0.0001	0.25	(0.12, 0.51)
Sens (8) – Loss to FU*	-	-	-	-	-	-	-	-	-	-	-
Sens (9) – Incorrect TF**	-	-	-	-	-	-	-	-	-	-	-

* No losses to follow-up observed so this sensitivity analysis is not applicable; ** No incorrect treatment failures observed, therefore this sensitivity analysis is not applicable.

Additional analyses

Development of uveitis in non-study eye

There were 43 (72%) patients who had unilateral vision in the adalimumab group and 22 (73%) patients in the placebo group. Those patients who had bilateral vision (17 [28%] in the adalimumab group and 8 [27%] in the placebo group) were not eligible for this analysis as they had uveitis in both eyes at baseline.

There were 5 (17%) placebo patients that developed uveitis (defined as sustained AC cell scores of 1+ or more over two consecutive visits) in the non-study eye and 1 (2%) adalimumab patient that developed uveitis in the non-study eye (the patient in the adalimumab group had baseline AC cells scores of 1+ in their non-eligible eye, but they were taking too many drops in this eye [left] for it to be eligible).

There were two patients (one adalimumab and one placebo) that had a single AC cell score of 1+ or more and were a treatment failure in their study eye at the same visit.

Time to treatment failure in both eyes

This analysis was not possible due to the fact that only one patient (placebo) failed in both eyes at different times.

Development of co-morbidity on treatment failure

There was one participant who developed cataract in the adalimumab group and none in the placebo group. Three participants developed IOP in the adalimumab group and none in the placebo group.

There were such few numbers in either of the two treatment groups who developed a co-morbidity, that any modelling including the development of a co-morbidity was not possible.

Post-hoc analyses

Time to treatment response

There was a total of 44 patients in the adalimumab group and eight patients in the placebo group who were classified as having a treatment response; the difference between the two groups was statistically significant (log-rank p-value = 0.002). The HR indicated that those patients on adalimumab were over three times more likely to achieve a treatment response than those on placebo, HR (95% CI) 3.01 (1.41 to 6.41).

Proportion of responders/failures/no change

Proportion of responders/failures/no change at three months

There was a total of 20 (35%) patients in the adalimumab group and 3 (10%) patients in the placebo group who were classified as having a treatment response prior to three months. The Cochran-Armitage trend test showed a significant difference between the treatment groups at three months, p=0.004.

There were three patients excluded from the analyses due to the fact that they had not reached the three-month time point.

Proportion of responders/failures/no change at six months

There was a total of 20 (37%) patients in the adalimumab group and 3 (11%) patients in the placebo group who were classified as having a treatment response prior to six months. The Cochran-Armitage trend test showed a significant difference between the treatment groups at six months, p=0.004.

There were nine patients excluded from the analyses due to the fact that they had not reached the six-month time point.

Area under the curve of AC cells in eligible eye

There was a significant difference in the median number of AC cells between the two groups -0.79 95% CI (-0.96, -0.63) p<0.0001, if favour of the adalimumab group. Similar results obtained when the best score or worst score was used for patients with two eligible eyes.