Open-label phase

Participants in the adalimumab group who were still on treatment at the point of the TSC decision to unblind subsequently took part in an open-label phase of the trial. Placebo participants moved straight to follow-up.

The tables that follow provide a summary of the open-label phase data.

Contents

Time to treatment failure

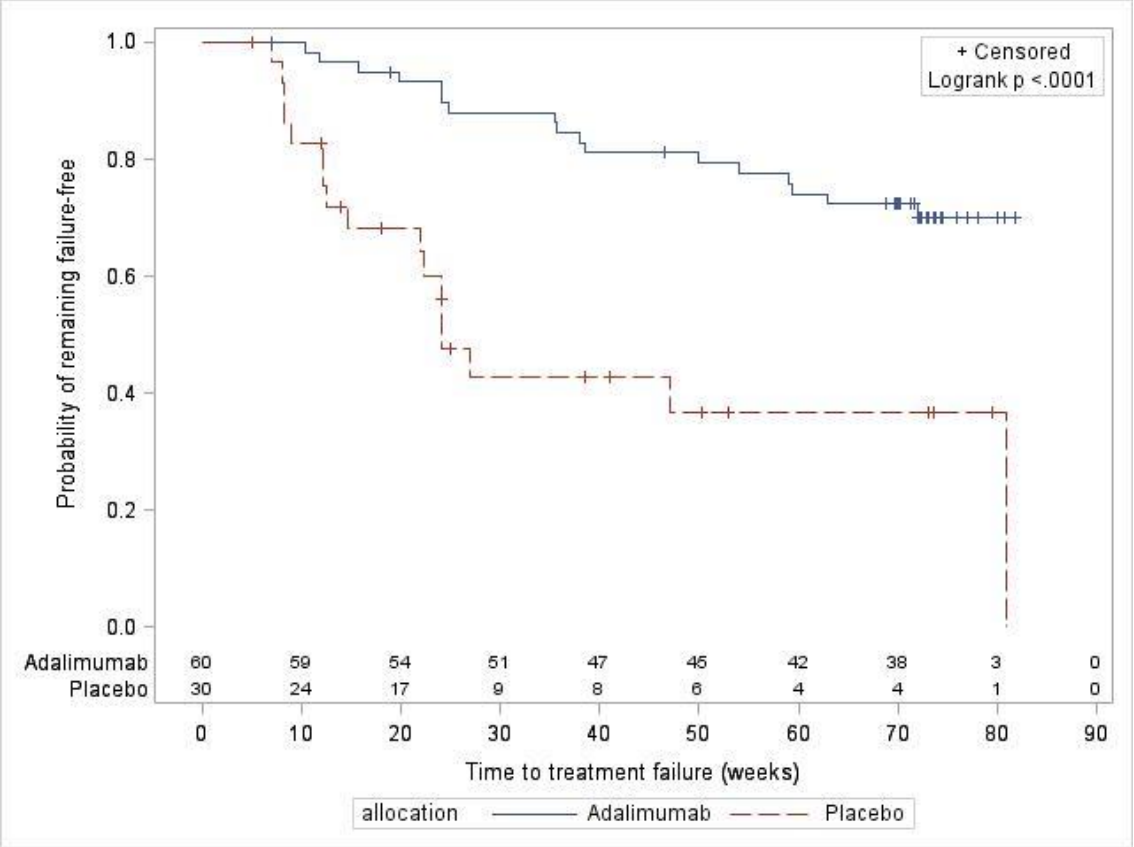
During the course of the open label phase of the trial, there were three additional treatment failures that occurred in the adalimumab arm.

In total, there were of 17 (28.3%) treatment failures for the 60 participants in the adalimumab group and 17 (56.7%) failures for the 30 participants in the placebo group. Median time to treatment failure was 24.1 weeks (95% CI 14.7 to 81) in the placebo group and was not reached in the adalimumab group within the 18-month treatment period because less than one-half of the subjects experienced treatment failure at the conclusion of the study.

The results of the logrank test from SAS PROC LIFETEST offered strong statistical evidence that the placebo group and adalimumab group differed with respect to time to treatment failure.

The HR indicated that treatment with adalimumab significantly decreased the hazard of treatment failure by 74% (HR=0.26, 95% CI (0.13 to 0.51), p<0.0001) relative to placebo.

Figure 1: Primary outcome Kaplan-Meier plot for blinded and open label phase



Sensitivity Analyses

Table 1 shows the results of the sensitivity analyses.

There were no losses to follow-up during the course of the trial and therefore sensitivity analysis eight was not conducted. The results of the other sensitivity analyses indicate that the original

conclusion from the primary analysis was robust with regards to the changes that were made. The overall statistical significance of the sensitivity analyses did not change.

Table 1: 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				
Sens (1) – best case	90	60	16	44	30	15	15	20.27	<0.0001	0.22	(0.10, 0.45)
Sens (2) – worst case	90	60	27	33	30	23	7	26.03	<0.0001	0.25	(0.14, 0.44)
Sens (3) – MTX	90	60	22	38	30	17	13	11.07	0.001	0.34	(0.18, 0.66)
Sens (4) – Component 1	90	60	17	43	30	17	13	17.41	<0.0001	0.25	(0.13, 0.51)
Sens (5) – Component 2	90	60	17	43	30	17	13	17.03	<0.0001	0.25	(0.13, 0.51)
Sens (6) – Component 3	90	60	17	43	30	17	13	16.92	<0.0001	0.26	(0.13,0.51)
Sens (7) – Missing PO	90	60	17	43	30	17	13	16.85	<0.0001	0.26	(0.13,0.51)
Sens (8) – Loss to FU*	90	-	-	-	-	-	-	-	-	-	-
Sens (9) – Incorrect TF	90	60	17	43	30	17	13	16.85	<0.0001	0.26	(0.13,0.51)

* No losses to follow-up observed so this sensitivity analysis is not applicable

Additional analyses

Development of uveitis in non-study eye

There were no further developments of uveitis in the non-study eye during the open label phase and therefore no further analysis was conducted.

Time to treatment failure in both eyes

There were no further events (treatment failure in both eyes) during the open label phase of the trial and therefore no further analysis was conducted.

Development of co-morbidity on treatment failure

There were no further developments of co-morbidity in the open-label phase of the trial, therefore no further analysis was possible.

Post-hoc analyses

Time to treatment response

During the open label phase of the trial three adalimumab participants achieved treatment response, meaning overall, there were 47 participants in the adalimumab group classified as having a treatment response; the difference between the two groups was statistically significant (log-rank p-value = 0.003) (Table 2). The HR indicated that those patients on adalimumab were just under three times more likely to achieve a treatment response than those on placebo, HR (95% CI) 2.96 (1.40 to 6.27).

Table 2: Time to treatment response

Analysis	N	Adalimumab			Placebo			Log-rank chi-square statistic	Log-rank p-value	HR	(95% CI)
		n	Treatment responses	Censored	n	Treatment responses	Censored				
ITT Time to treatment response	90	60	47	13	30	8	22	9.05	0.003	2.96	(1.40, 6.27)

Proportion of responders/failures/no change

Proportion of responders/failures/no change at three months

The results from this section are from the integrated analysis of the double blind and open label data for the adalimumab group versus the double blind data for the placebo group.

There was a total of 20 (33.9%) patients in the adalimumab group and 3 (10.3%) 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 = 0.0043 (Table 3).

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

Table 3: Proportion of responders/failures/no change at three months

	Adalimumab	Placebo	Total	Cochran-Armitage trend test p-value
Treatment failure prior to 3 months	1 (1.7%)	4 (13.8%)	5 (5.7%)	0.0043
Neither a treatment failure nor treatment response prior to 3 months	38 (64.4%)	22 (75.9%)	60 (68.2%)	
Treatment response prior to 3 months	20 (33.9%)	3 (10.3%)	23 (26.1%)	
Total	**59**	**29**	**88**	

Proportion of responders/failures/no change at six months

The results from this section are from the integrated analysis of the double blind and open label data for the adalimumab group versus the double blind data for the placebo group.

There was a total of 20 (34.5%) patients in the adalimumab group and 3 (11.1%) patients in the placebo group who were classified as having a treatment response prior to six months (Table 4). The Cochran-Armitage trend test showed a significant difference between the treatment groups at six months, p = 0.0041.

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

Table 4: Proportion of responders/failures/no change at six months

	Adalimumab	Placebo	Total	Cochran-Armitage trend test p-value
Treatment failure prior to 6 months	1 (1.7%)	4 (14.8%)	5 (5.9%)	0.0041
Neither a treatment failure nor treatment response prior to 6 months	37 (63.8%)	20 (74.1%)	57 (67.1%)	
Treatment response prior to 6 months	20 (34.5%)	3 (11.1%)	23 (27.1%)	
Total	**58**	**27**	**85**	

Area under the curve of AC cells in eligible eye

The results from this section are from the integrated analysis of the double blind and open label data for the adalimumab group versus the double blind data for the placebo group.

The AUC of AC cells is shown in Table 5. There was a significant difference in the medians between the two groups, with similar results obtained when the best score or worst score was used for patients with two eligible eyes.

Table 5: AUC for AC cells of eligible eyes

	Adalimumab	Placebo	Total	Difference in medians* (95% CI) p-value#
Eye-level				
N	77	38	115	
Median	0.22	1.04	0.42	-0.81
Interquartile range	(0.11, 0.46)	(0.79, 1.67)	(0.14, 0.92)	(-0.99, -0.64)
Minimum	0.03	0.08	0.03	p<0.0001
Maximum	2.00	3.00	3.00	
Best-case				
N	60	30	90	
Median	0.20	1.00	0.37	-0.75
Interquartile range	(0.09, 0.40)	(0.70, 1.67)	(0.14, 0.79)	(-0.94, -0.57)
Minimum	0.03	0.08	0.03	p<0.0001
Maximum	1.07	3.00	3.00	
Worst-case				
N	60	30	90	
Median	0.23	1.09	0.38	-0.82
Interquartile range	(0.11,0.44)	(0.79, 1.67)	(0.17, 0.97)	(-1.03, -0.60)
Minimum	0.03	0.08	0.03	p<0.0001
Maximum	2.00	3.00	3.00	

* Difference in medians calculated using the Hodges-Lehman estimate with the Moses distribution-free 95% CI.
# Non-parametric two-sample Mann-Whitney test for a difference in medians.

Number of participants failing treatment

There were seventeen participants in the adalimumab group (28.33%) (integrated analysis of the double blind and open label data) and 17 participants in the placebo group (56.67%) (double blind phase alone) who were classified as treatment failures. The risk of having a treatment failure was significantly reduced by 54% (RR=0.46, 95% CI (0.26 to 0.83); p=0.01) in the adalimumab group compared to placebo (Table 6).

Table 6: Number of treatment failures

Treatment	Number randomised	Number of treatment failures N (%)	Relative risk (95% CI)	P-value
Placebo	30	17 (56.67%)	0.46 (0.26-0.83)	0.01
Adalimumab	60	17 (28.33%)		
Total	**90**	**34 (37.78%)**		

Total oral corticosteroid dose

This analysis only included patients who were on oral corticosteroids at the beginning of the double blind phase. The analysis integrates data from adalimumab patients collected during the double blind phase and the open label phase and compares it to the placebo patients (double blind data only).

The total oral corticosteroid use during the open label phase is shown in Table 7.

Table 7: Total oral corticosteroid use during the open label phase

Treatment	Number randomised	Received oral corticosteroids	Total oral corticosteroid dose (mg) during open label	Total time on study treatment during open label	Standardised dose per patient year during open label phase
Adalimumab	60	1	19	0.75	25.33

A total of one participant in the placebo group and 5 participants in the adalimumab group were taking oral corticosteroids at the beginning of the double blind phase of the study. The 5 participants in the adalimumab group were on study treatment for a total of 6.03 years and the placebo participant was on study treatment for 0.17 years (Table 8).

The integrated analysis of total oral dose, standardised per patient year, was 3767.74 mg in the placebo group and 707.70 mg in the adalimumab group. A rate ratio of 0.19 (95% CI [0.17, 0.20]) indicated that patients on placebo required more oral corticosteroids per patient year than those on adalimumab and there was evidence at the 5% level of a statistically significant difference between the two groups (Table 8).

Table 8: Total oral corticosteroid dose: Integrated analysis

Treatment	Number randomised	Received oral corticosteroids	Total oral corticosteroid dose (mg)	Total time on study treatment – years	Total oral dose (mg) standardised to per patient year	Rate ratio (95% CI)	p-value
Placebo	30	1	640	0.17	3767.74	0.19 (0.17,0.20)	<0.0001
Adalimumab	60	5	4267.5	6.03	707.70		

Rate of systemic corticosteroid dose from entry dose

This analysis only included patients who were on systemic corticosteroids at the beginning of the double blind phase. The analysis integrates data from adalimumab patients collected during the double blind phase and the open label phase and compares it to the placebo patients (double blind data only).

The result of this analysis was the same as that of the total oral corticosteroid analysis.

Reduction in systemic corticosteroid dose from entry dose to 0mg

There was one patient who reached 0mg during the open label phase. The line listing for this patient is given in Table 9.

Table 9: Line listing for patient on systemic corticosteroid during open label phase

Randomisation number	Randomisation date	End date	Unblinding date	Total days on systemic steroids
0540080	20OCT2014	22/06/2015	03/06/2015	245

At randomisation, six participants (5 adalimumab, 1 placebo) were on systemic corticosteroids (permitted dose: <0.2mg/kg/day; median dose, 0.14mg/kg; median dose for adalimumab, 0.15mg/kg; median dose for placebo, 0.14mg/kg). Four adalimumab-treated participants stopped systemic corticosteroids (median duration 18.4 weeks). The placebo patient stopped systemic corticosteroids after 5.6 weeks. The planned analysis was not able to be performed due to the fact that statistical algorithm did not converge (Table 10).

Table 10: Reduction in systemic corticosteroid to 0 mg/day

Treatment	**Number randomised**	**Number included in analysis**	**HR (95% CI)**	**p-value**
Placebo	30	1	-	-
Adalimumab	60	5		

Reduction in systemic corticosteroid dose from entry dose to <5mg

There were no patients who reached 5mg during the open label phase.

At randomisation there were three participants (two in the adalimumab group and one in the placebo group) who were on ≥ 5 mg of systemic corticosteroids. No participants who were receiving ≥ 5 mg systemic corticosteroids at randomisation experienced treatment failure whilst receiving ≥ 5 mg systemic corticosteroids.

The planned analysis was not able to be performed due to the fact that statistical algorithm did not converge (Table 11).

Table 11: Reduction in systemic corticosteroid to 5 mg/day

Treatment	Number randomised	Number included in analysis	HR (95% CI)	p-value
Placebo	30	1	-	-
Adalimumab	60	2		

Time to reduction to <2 drops in topical corticosteroids

The outcome was time to reduction to < 2 drops for those participants already at ≥ 2 drops at randomisation. There were 63 participants who were on ≥ 2 drops at randomisation (18 [60%] in the placebo group and 45 [75%] in the adalimumab group) and, therefore, included in the integrated analysis of the double blind and open label data for the adalimumab group versus the double blind data from the placebo group.

There were five patients who had topical corticosteroids of >=2drops at baseline and also during the open label phase (Table 12). There was one patient who reached <2 drops during the open label phase.

The time to reduction to <2 drops was statistically significant in favour of adalimumab, HR (95% CI) 4.25 (1.26, 14.30), p=0.02 (Table 13).

Twenty five (55.6%) of the 45 patients on adalimumab and three (16.7%) of the 18 patients on placebo reached < 2 drops before treatment failure or before reaching the 18 months treatment visit, nine patients (20%) on adalimumab and one (5.6%) patient on placebo reached the 18 month visit before reaching < 2 drops and 11 (24.4%) of the adalimumab group and 14 (77.8%) of the placebo group had a treatment failure/withdrawal before reaching < 2 drops.

Table 12: Patients who had topical corticosteroids of >=2drops at baseline and also during the open label phase

Randomisation number	Randomisation date	End date	Unblinding date	Total days on topical steroids
0036081	20/11/2014	04/04/2016	27/04/2015	501
0124087	05/01/2015	18/05/2016	11/05/2015	499
0249083	05/12/2014	22/04/2016	22/05/2015	504
0249091	27/03/2015	11/09/2015	24/04/2015	168
0540080	20/10/2014	02/03/2016	03/06/2015	499

Table 13: Time to reduction to < 2 drops

Treatment	Number randomised	Number included in analysis	HR for reduction to < 2 drops (95% CI)	p-value	HR treatment failure (95% CI)	p-value
Placebo	30	18 (60)	-	-	-	-
Adalimumab	60	45 (75)	4.25 (1.26, 14.3)	0.02	0.20 (0.09,0.43)	<0.0001

Time to reduction to 0 drops in topical corticosteroids (post-hoc analysis)

The outcome was time to reduction to 0 drops for those participants already at > 0 drops at randomisation. There were 74 participants (25 [33.8%] on placebo and 49 [66.2%] on adalimumab) who were on > 0 drops at randomisation and, therefore, included in the integrated analysis of the double blind and open label data for the adalimumab group versus the double blind data from the placebo group.

There were 8 patients who had topical corticosteroids of >0 drops at baseline and also during the open label phase (Table 14). In the open label period, one more patient reached 0 drops.

The time to reduction to 0 drops was statistically significant in favour of Adalimumab, HR 4.26 (95% CI) (1.49, 12.2), p = 0.0068.

Twenty six (53.12%) of the 49 patients on adalimumab and four (16%) of the 25 patients on placebo reached 0 drops before treatment failure or before reaching the 18-month treatment visit, twelve participants (24.5%) on adalimumab and two participants (8%) on placebo reached the 18 month visit before reaching 0 drops and 11 (22.5%) of the adalimumab group and 19 (76%) of the placebo group had a treatment failure/withdrawal before reaching 0 drops.

Table 14: Patients who had topical corticosteroids of >0 drops at baseline and also during the open label phase

Randomisation number	Randomisation date	End date	Unblinding date	Total days on topical steroids
0036081	20/11/2014	04/04/2016	27/04/2015	501
0116072	10/07/2014	26/11/2015	06/05/2015	504
0243089	10/02/2015	03/06/2015	06/05/2015	113
0248087	05/01/2015	18/05/2016	11/05/2015	499
0249065	25/04/2014	11/09/2015	15/05/2015	504
0249083	05/12/2014	22/04/2016	22/05/2015	504
0249091	27/03/2015	11/09/2015	24/04/2015	168
0540080	20/10/2014	02/03/2016	03/06/2015	499

Table 15: Time to reduction to 0 drops

Treatment	**Number randomised**	**Number included in analysis**	**HR for reduction to 0 drops (95% CI)**	**p-value**	**HR treatment failure (95% CI)**	**p-value**
Placebo	30	25 (34%)	-	-	-	-
Adalimumab	60	49 (66%)	4.26 (1.49,12.2)	0.0068	0.18 (0.09,0.38)	<0.0001

Time to reduction to 0 drops in topical corticosteroids

There were no additional patients who required pulsed corticosteroids during the open label phase.

There was one participant in the placebo group (3.33%) and two participants in the adalimumab group (3.33%) who required pulsed corticosteroids during the course of the double blind and open label phase of the trial. There was no evidence (p = 1.00) of a difference in the risk of requiring pulsed corticosteroids between the two treatment groups (Table 16).

Table 16: Number of patients requiring pulsed corticosteroids

Treatment	**Number randomised**	**Number needing pulsed corticosteroids, N (%)**
Placebo	30	1 (3.33)
Adalimumab	60	2 (3.33)
Total	90	3 (3.33)
	Relative risk (95% CI)	**p-value**
	1.0 (0.09, 10.59)	1.00

Optic and Ocular: Number of participants with disease flares following a minimum of 3 months of disease control

There were no further events of disease flare following disease control within the open label phase, therefore, no integrated analysis of the double blind and open label data was conducted.

Optic and Ocular: Number of participants with disease flares within the first 3 months of the study

One participant in the adalimumab arm failed within the open label phase of the study.

There were three participants in the placebo group (10%) (double blind phase only) and one participant in the adalimumab group (3.33%) who had a disease flare in the first three months of treatment. There was no statistically significant evidence at the 5% level (p=0.11) of a difference (RR 0.17, 95% CI (0.02, 1.54)) between the two groups (Table 17).

No participants in the placebo group who had a flare were eligible on two eyes; therefore, the analysis on both eyes was not possible.

Table 17: Number of participants having disease flares in the first three months in at least one eligible eye

Treatment	Number randomised	Number experiencing disease flares, N (%)	Relative risk of experiencing disease flares (95% CI)	Fisher's Exact Test P-value	Number experiencing disease flares who later failed treatment as defined by PO, N (%)
Placebo	30	3* (10.00%)	0.17 (0.02, 1.54)	0.11	1 (3.33%)
Adalimumab	60	1* (3.33%)			1 (1.67%)
Total	**90**	**4 (4.44%)**			**2 (2.22%)**

*No patients were eligible in both eyes.

Optic and Ocular: Visual acuity as measured by age appropriate LogMAR assessment

Table 18 presents summary data for the integrated analysis of the double blind and open label data for the adalimumab group and the double blind phase for the placebo group.

Table 18: LogMAR Score by treatment group at each time-point

* 1 patient with unobtainable data

Visit	Treatment																	
	Adalimumab						Placebo						Total					
	Best Score			Worst Score			Best Score			Worst Score			Best Score			Worst Score		
	n	Mean (SD)	Median (Range)	n	Mean (SD)	Median (Range)	n	Mean (SD)	Median (Range)	n	Mean (SD)	Median (Range)	n	Mean (SD)	Median (Range)	n	Mean (SD)	Median (Range)
Baseline	60	0.04 (0.15)	0.00 (-0.23, 0.56)	60	0.05 (0.16)	0.00 (-0.23, 0.56)	30	0.06 (0.12)	0.05 (-0.13, 0.40)	30	0.08 (0.12)	0.06 (-0.10, 0.40)	90	0.04 (0.14)	0.00 (-0.23, 0.56)	90	0.06 (0.14)	0.03 (-0.23, 0.56)
1 month	60	0.03 (0.17)	0.00 (-0.30, 0.80)	60	0.04 (0.18)	0.00 (-0.30, 0.80)	30	0.02 (0.16)	0.00 (-0.28, 0.38)	30	0.06 (0.17)	0.04 (-0.28, 0.38)	90	0.02 (0.17)	0.00 (-0.30, 0.80)	90	0.05 (0.18)	0.00 (-0.30, 0.80)
2 months	58 *	0.02 (0.17)	0.00 (-0.20, 0.56)	58 *	0.04 (0.19)	0.00 (-0.20, 0.75)	25	0.05 (0.18)	0.00 (-0.15, 0.76)	25	0.06 (0.18)	0.02 (-0.15, 0.76)	83 *	0.03 (0.17)	0.00 (-0.20, 0.76)	83 *	0.04 (0.19)	0.00 (-0.20, 0.76)
3 months	57	0.00 (0.16)	0.00 (-0.20, 0.80)	57	0.02 (0.19)	0.00 (-0.20, 0.88)	19	0.01 (0.11)	0.00 (-0.13, 0.24)	19	0.03 (0.12)	0.00 (-0.13, 0.28)	76	0.00 (0.14)	0.00 (-0.20, 0.80)	76	0.02 (0.18)	0.00 (-0.20, 0.88)
6 months	51 *	0.02 (0.19)	-0.02 (-0.20, 0.88)	51 *	0.02 (0.19)	0.00 (-0.20, 0.88)	12	0.05 (0.16)	0.02 (-0.18, 0.30)	12	0.07 (0.19)	0.02 (-0.18, 0.38)	63 *	0.02 (0.18)	0.00 (-0.20, 0.88)	63 *	0.03 (0.19)	0.00 (-0.20, 0.88)
9 months	48	-0.01 (0.14)	0.00 (-0.25, 0.40)	48	-0.01 (0.14)	0.00 (-0.25, 0.40)	7	0.00 (0.17)	-0.08 (-0.10, 0.36)	7	0.04 (0.20)	-0.08 (-0.10, 0.36)	55	-0.01 (0.14)	0.00 (-0.25, 0.40)	55	0.00 (0.14)	0.00 (-0.25, 0.40)
12 months	43	-0.02 (0.14)	-0.02 (-0.23, 0.34)	43	-0.01 (0.14)	0.00 (-0.23, 0.34)	5	0.03 (0.14)	0.02 (-0.10, 0.26)	5	0.08 (0.17)	0.03 (-0.10, 0.26)	48	-0.02 (0.14)	-0.01 (-0.23, 0.34)	48	0.00 (0.14)	0.00 (-0.23, 0.34)
15 months	38	-0.01 (0.12)	0.00 (-0.25, 0.40)	38	0.00 (0.12)	0.00 (-0.25, 0.40)	3	0.00 (0.26)	-0.10 (-0.20, 0.30)	3	0.00 (0.26)	-0.10 (-0.20, 0.30)	41	-0.01 (0.13)	0.00 (-0.25, 0.40)	41	0.00 (0.13)	0.00 (-0.25, 0.40)
18 months	34	0.00 (0.13)	0.00 (-0.22, 0.28)	34	0.01 (0.12)	0.00 (-0.22, 0.28)	3	0.02 (0.21)	-0.10 (-0.10, 0.26)	3	0.02 (0.21)	-0.10 (-0.10, 0.26)	37	0.00 (0.13)	0.00 (-0.22, 0.28)	37	0.01 (0.12)	0.00 (-0.22, 0.28)

Table 19 presents data for the open label phase for the adalimumab group.

Table 19: LogMAR Score at each time-point (Open label)

	Adalimumab					
	Best Score			Worst Score		
Visit	n	Mean (SD)	Median (Range)	n	Mean (SD)	Median (Range)
Baseline	-	-	-	-	-	-
1 month	-	-	-	-	-	-
2 months	1	0.00 (N/A)	0.00 (0.00, 0.00)	1	0.00 (N/A)	0.00 (0.00, 0.00)
3 months	1	-0.04 (N/A)	-0.04 (-0.04,-0.04)	1	-0.02 (N/A)	-0.02 (-0.02,-0.02)
6 months	4	0.01 (0.07)	-0.02 (-0.05, 0.10)	4	0.01 (0.07)	-0.02 (-0.05, 0.10)
9 months	6	-0.01 (0.14)	0.02 (-0.20, 0.20)	6	0.00 (0.15)	0.03 (-0.20, 0.20)
12 months	9	-0.05 (0.13)	-0.05 (-0.20, 0.20)	9	-0.05 (0.13)	-0.05 (-0.20, 0.20)
15 months	11	-0.01 (0.09)	0.00 (-0.15, 0.16)	11	-0.01 (0.10)	0.00 (-0.15, 0.16)
18 months	11	-0.04 (0.12)	-0.03 (-0.22, 0.20)	11	-0.04 (0.13)	-0.03 (-0.22, 0.20)

The data used for the joint modelling was from the integrated analysis of the double blind and open label phase for the adalimumab group and the double blind phase for the placebo group (Table 20 and Table 21).

Two analyses were conducted using joint modelling, in each analysis, when only one eye is involved; the single LogMAR value is used. When there are two eyes involved, the two analyses are:

Analysis 1 -Taking the best LogMAR measurement (the minimum of the 2 values).

Analysis 2- Taking the worst LogMAR measurement (the maximum of the 2 values)

Table 20: Model Parameters for Joint Modelling of LogMAR Analysis 1

Component	Parameter	Estimate	95%Lower	95%Upper	P-value
Longitudinal	(Intercept)	0.01	-0.03	0.04	0.76
	Baseline	0.70	0.51	0.92	<0.0001
	Time	-0.002	-0.004	4e-04	0.17
	Adalimumab	-0.01	-0.06	0.02	0.53
Survival	Adalimumab	-1.33	-2.25	-0.73	0.001
	HR	0.26	0.11	0.48	0.001
Association	γ_0	2.86	-2.41	10.37	0.41

Table 21: Model Parameters for Joint Modelling of LogMAR Analysis 2

Component	Parameter	Estimate	95%Lower	95%Upper	P-value
Longitudinal	(Intercept)	0.02	-0.02	0.05	0.37
	Baseline	0.81	0.60	1.06	<0.0001
	Time	-0.002	-0.004	3e-04	0.17
	Adalimumab	-0.02	-0.07	0.02	0.37
Survival	Adalimumab	-1.32	-2.23	-0.70	0.001
	HR	0.27	0.11	0.50	0.001
Association	γ_0	3.31	-2.14	8.43	0.27

Optic and Ocular: Number of participants with resolution of associated optic nerve

There were no further events of resolution of optic nerve within the open label phase. Therefore, no integrated analysis of the double blind and open label data was conducted.

Optic and Ocular: Number of participants with resolution of macular oedema

There were no further events of resolution of macular oedema within the open label phase. Therefore, no integrated analysis of the double blind and open label data was conducted.

Optic and Ocular: Number of participants with disease control for 3 months

There were four patients (6.7%) in the adalimumab group who had disease control in at least one eligible eye for at least three months in the open label phase of the trial (Table 22).

Table 22: Line listing of additional participants with disease control in at least one eligible eye for at least 3 months in the open-label phase

Participant	Date of randomisation	Eligible eye	Date of unblinding	Period of disease control
0116068	05-Jun-14	Left eye	07-May-15	28-Aug-14 to 18-Jun-15
0243089	10-Feb-15	Left eye	06-May-15	11-Mar-15 to 29-Jun-16
0248087	05-Jan-15	Both eyes	11-May-15	07-Sep-15 to 25-Feb-16
0249065	25-Apr-14	Right eye	15-May-15	10-Oct-14 to 11-Sep-15

There were four patients (6.7%) in the adalimumab group who had disease control in all eligible eyes for at least three months in the open label phase of the trial (Table 23).

Table 23: Line listing of additional participants with disease control in all eligible eyes for at least 3 months in the open-label phase

Participant	Date of randomisation	Eligible eye	Date of unblinding	Period of disease control
0116068	05-Jun-14	Left eye	07-May-15	28-Aug-14 to 18-Jun-15
0243089	10-Feb-15	Left eye	06-May-15	11-Mar-15 to 29-Jun-16
0248087	05-Jan-15	Both eyes	11-May-15	07-Sep-15 to 25-Feb-16
0249065	25-Apr-14	Right eye	15-May-15	10-Oct-14 to 11-Sep-15

The following analysis is for the integrated analysis of the double blind and open label data from the adalimumab group versus the double blind data from the placebo group.

Two participants in the placebo group (6.67%) and 27 in the adalimumab group (45.00%) had disease control for at least three months (RR=6.75, 95% CI [1.72 to 26.51], p=0.0002) (Table 24).

One (50.00%) of the 2 participants with disease control in the placebo group had both eyes eligible at baseline but did not have disease control in both eyes. Of the 27 participants in the adalimumab group, 7 participants (25.93%) (Table 24) had both eyes eligible at baseline and all 7 participants had disease control in both study eyes for at least three months (Table 25).

Table 24: Disease control for at least three months in at least one eligible eye

Treatment	Number randomised	Number with disease control, N (%)	Relative risk (95% CI)	Fisher's Exact Test P-value
Placebo	30	2* (6.67%)	6.75 (1.72, 26.51)	0.0002
Adalimumab	60	27** (45.00%)		
Total	**90**	**29 (32.22%)**		

*1 (50.00%) participant was eligible in both eyes

**7 (25.93%) participants were eligible in both eyes

Table 25: Disease control for at least three months in all eligible eyes

Treatment	Number randomised	Number with disease control, N (%)	Relative risk (95% CI)	Fisher's Exact Test P-value
Placebo	30	1 (3.33%)	13.50 (1.93, 94.62)	<0.0001
Adalimumab	60	27 (45.00%)		
Total	**90**	**28 (31.11%)**		

Number of participants with disease control for 6 months

Five participants in the adalimumab group had disease control in at least one eligible eye for at least six months in the open label phase of the study (Table 26).

Table 26: Line listing of additional participants with disease control in at least one eligible eye for at least 6 months in the open-label phase

Participant	Date of randomisation	Eligible eye	Date of unblinding	Period of disease control
0116068	05-Jun-14	Left eye	07-May-15	28-Aug-14 to 18-Jun-15
0243089	10-Feb-15	Left eye	06-May-15	11-Mar-15 to 29-Jun-16
0248087	05-Jan-15	Both eyes	11-May-15	07-Sep-15 to 25-Feb-16
0249083	05-Dec-14	Right eye	22-May-15	30-Jan-15 to 22-Apr-16
0540080	20-Oct-14	Right eye	03-Jun-15	14-Jan-15 to 02-Mar-16

Of the 5 participants who had disease control for at least 6 months in the open label phase, 1 was eligible in both eyes and had disease control in both eyes (Table 27).

Table 27: Line listing of additional participants with disease control in all eligible eyes for at least 6 months in the open-label phase

Participant	Date of randomisation	Eligible eye	Date of unblinding	Period of disease control
0116068	05-Jun-14	Left eye	07-May-15	28-Aug-14 to 18-Jun-15
0243089	10-Feb-15	Left eye	06-May-15	11-Mar-15 to 29-Jun-16
0248087	05-Jan-15	Both eyes	11-May-15	07-Sep-15 to 25-Feb-16
0249083	05-Dec-14	Right eye	22-May-15	30-Jan-15 to 22-Apr-16
0540080	20-Oct-14	Right eye	03-Jun-15	14-Jan-15 to 02-Mar-16

At six months, one participant (3.33%) in the placebo group and 22 participants in the adalimumab group (36.67%) had disease control in at least one of their eligible eyes (RR = 11.00, 95% CI [1.56 to 77.74]; p=0.0003) (Table 28).

Table 28: Disease control for at least six months in at least one eligible eye

Treatment	Number randomised	Number with disease control, N (%)	Relative risk (95% CI)	Fisher's Exact Test P-value
Placebo	30	1 (3.33%)	11.00 (1.56, 77.74)	0.0003
Adalimumab	60	22* (36.67%)		
Total	**90**	**23 (25.56%)**		

*5 (22.73%) patients were eligible in both eyes

Five of the 22 (22.73%) in the adalimumab group had two eyes eligible at the beginning of the study. All 5 participants had disease control in both eyes for at least 6 months (

Table 29).

Table 29: Disease control for at least six months in all eligible eyes

Treatment	Number randomised	Number with disease control, N (%)	Relative risk (95% CI)	Fisher's Exact Test P-value
Placebo	30	1 (3.33%)	11.00 (1.56, 77.74)	0.0003
Adalimumab	60	22 (36.67%)		
Total	**90**	**23 (25.56%)**		

Optic and Ocular: Number of participants entering disease remission for 3 months

There were no further events of disease remission for 3 months within the open label phase. Therefore, no integrated analysis of the double blind and open label data was conducted.

Optic and Ocular: Number of participants entering disease remission for 6 months

There were no further events of disease remission for 6 months within the open label phase. Therefore, no integrated analysis of the double blind and open label data was conducted.

Optic and Ocular: Duration of sustaining inactive disease

This analysis combined data from the double blind phase with the open label phase for the adalimumab group and compared it to the placebo group (double blind only).

The difference in total amount of time participants sustained inactive disease was statistically significant between the two treatment groups, with participants in the adalimumab group spending approximately 209 more days with inactive disease than those in the placebo group (p<0.0001) (Table 30).

Table 30: Duration of sustaining inactive disease by treatment group

Treatment	Number randomised	Estimated mean days of sustained inactive disease (SE)	Estimated treatment effect (95% CI)	P-value
Placebo	30	16.31 (25.69)	209.12 (144.20, 274.05)	<0.0001
Adalimumab	60	225.43 (18.15)		

Quality of life assessments: CHQ

The summary statistics for each time point for CHQ PsS (integrated analysis of the double blind and open label phase for the adalimumab group and double blind phase for the placebo group) and the parameter estimates are given in Tables 31 and 32, respectively. The open-label phase data is shown in Table 33.

Table 31: CHQ Psychosocial – PsS Summary Statistics by treatment by timepoint

	Adalimumab				Placebo				Total			
Visit	n	missing	Mean (SD)	Median (range)	n	missing	Mean (SD)	Median (range)	n	missing	Mean (SD)	Median (range)
Baseline	53	7	51.17 (9.53)	52.74 (30.69,65.85)	22	8	49.48 (7.55)	49.67 (37.25,60.76)	75	15	50.68 (8.98)	51.99 (30.69,65.85)
1 month	53	7	51.06 (10.36)	53.41 (18.72,65.19)	27	3	50.01 (10.27)	50.58 (20.75,63.60)	80	10	50.71 (10.28)	53.24 (18.72,65.19)
2 months	50	9	53.16 (9.94)	55.91 (24.01,64.52)	19	6	50.20 (10.75)	52.42 (30.57,64.29)	69	15	52.34 (10.17)	54.62 (24.01,64.52)
3 months	51	6	54.13 (8.93)	57.41 (26.86,64.30)	16	3	54.21 (8.57)	55.38 (38.63,64.47)	67	9	54.15 (8.78)	57.23 (26.86,64.47)
6 months	42	10	54.07 (9.57)	57.00 (15.14,65.20)	11	1	49.68 (11.56)	54.18 (23.16,61.32)	53	11	53.16 (10.06)	56.19 (15.14,65.20)
9 months	39	9	56.18 (6.74)	58.04 (39.68,66.12)	7	0	50.26 (13.72)	56.14 (25.06,62.08)	46	9	55.28 (8.25)	56.93 (25.06,66.12)
12 months	42	1	55.05 (8.73)	57.55 (27.32,65.36)	4	1	54.18 (8.83)	55.36 (42.61,63.39)	46	2	54.98 (8.65)	57.55 (27.32,65.36)
15 months	36	2	55.21 (7.38)	56.25 (36.75,65.35)	3	0	53.27 (11.83)	55.45 (40.50,63.87)	39	2	55.06 (7.60)	55.73 (36.75,65.35)
18 months	30	4	54.75 (10.41)	56.73 (10.02,65.62)	3	0	47.25 (18.64)	55.49 (25.91,60.35)	33	4	54.07 (11.16)	55.66 (10.02,65.62)

Table 32: Joint modelling results for PsS summary score

Component	Parameter	Estimate	95% Lower	95% Upper	P-value
Longitudinal	(Intercept)	15.37	6.54	22.59	0.0004
	Baseline	0.69	0.55	0.85	<0.0001
	Time	0.08	-0.10	0.23	0.34
	Adalimumab	2.37	-0.41	5.47	0.14
Survival	Adalimumab	-1.56	-2.45	-0.85	0.0002
	HR	0.21	0.09	0.43	0.0002
Association	γ_0	-0.11	-0.24	-0.01	0.07

Table 33: CHQ Psychosocial– PsS Summary Statistics by treatment by timepoint (Open label)

	Adalimumab			
Visit	n	missing	Mean (SD)	Median (range)
Baseline	-	-	-	-
1 month	-	-	-	-
2 months	1	0	59.69 (N/A)	59.69 (59.69,59.69)
3 months	1	0	54.54 (N/A)	54.54 (54.54,54.54)
6 months	2	2	56.77 (1.64)	56.77 (55.61,57.93)
9 months	4	2	59.36 (5.46)	58.90 (53.51,66.12)
12 months	9	0	58.61 (5.72)	57.48 (51.00,65.36)
15 months	11	0	58.96 (4.87)	60.85 (49.66,64.66)
18 months	10	1	57.08 (7.09)	60.35 (46.19,65.62)

The summary statistics for each time point for CHQ PhS (integrated analysis of the double blind and open label phase for the adalimumab group and double blind phase for the placebo group) and parameter estimates are given in Tables 34 and 35, respectively. The open-label phase data is shown in Table 36.

Table 34: CHQ Physical -PhS Summary Statistics by treatment by time point

	Adalimumab				**Placebo**				**Total**			
Visit	n	missing	Mean (SD)	Median (range)	n	missing	Mean (SD)	Median (range)	n	missing	Mean (SD)	Median (range)
Baseline	53	7	43.20 (11.84)	46.39 (-3.81,59.97)	22	8	40.48 (16.36)	43.54 (6.44,58.87)	75	15	42.40 (13.26)	46.28 (-3.81,59.97)
1 month	53	7	45.54 (11.29)	47.61 (1.97,61.07)	27	3	44.73 (12.10)	49.02 (7.47,59.60)	80	10	45.27 (11.50)	47.69 (1.97,61.07)
2 months	50	9	47.57 (10.58)	51.95 (10.96,59.65)	19	6	43.65 (15.56)	46.85 (-2.61,59.65)	69	15	46.49 (12.16)	51.77 (-2.61,59.65)
3 months	51	6	46.59 (13.02)	51.23 (3.62,60.76)	16	3	47.35 (7.97)	48.89 (31.61,59.65)	67	9	46.77 (11.95)	49.83 (3.62,60.76)
6 months	42	10	47.58 (11.71)	52.86 (9.30,58.64)	11	1	41.95 (15.79)	43.69 (1.20,59.65)	53	11	46.41 (12.70)	50.46 (1.20,59.65)
9 months	39	9	48.10 (10.97)	52.45 (11.12,59.00)	7	0	45.20 (14.77)	51.67 (22.56,57.01)	46	9	47.66 (11.48)	52.06 (11.12,59.00)
12 months	42	1	48.87 (11.98)	53.22 (3.54,59.53)	4	1	53.09 (4.79)	54.07 (46.83,57.40)	46	2	49.23 (11.56)	53.22 (3.54,59.53)
15 months	36	2	46.51 (14.41)	51.71 (6.03,60.05)	3	0	55.75 (2.48)	54.86 (53.83,58.55)	39	2	47.22 (14.06)	52.18 (6.03,60.05)
18 months	30	4	48.44 (10.66)	52.22 (17.26,59.02)	3	0	53.77 (9.71)	59.09 (42.56,59.65)	33	4	48.93 (10.55)	52.78 (17.26,59.65)

Table 35: Joint modelling analysis results of PhS summary score

Component	Parameter	Estimate	95% Lower	95% Upper	P-value
Longitudinal	(Intercept)	20.68	12.17	30.70	<0.0001
	Baseline	0.58	0.38	0.75	<0.0001
	Time	0.04	-0.11	0.16	0.56
	Adalimumab	1.23	-2.31	5.28	0.53
Survival	Adalimumab	-1.34	-2.30	-0.67	0.001
	HR	0.26	0.10	0.51	0.001
Association	γ_0	-0.05	-0.15	0.03	0.24

Table 36: CHQ Physical– PhS Summary Statistics by treatment by time point (Open label)

	Adalimumab			
Visit	n	missing	Mean (SD)	Median (range)
Baseline	-	-	-	-
1 month	-	-	-	-
2 months	1	0	49.10 (N/A)	49.10 (49.10,49.10)
3 months	1	0	51.23 (N/A)	51.23 (51.23,51.23)
6 months	2	2	56.01 (2.82)	56.01 (54.02,58.00)
9 months	4	2	53.32 (6.92)	55.34 (43.86,58.75)
12 months	9	0	54.65 (2.17)	54.89 (51.46,57.35)
15 months	11	0	54.84 (3.38)	55.21 (49.14,58.98)
18 months	10	1	53.50 (4.07)	53.76 (47.56,59.02)

Quality of life assessments: CHAQ

The summary statistics for the CHAQ (integrated analysis of the double blind and open label phase for the adalimumab group and double blind phase for the placebo group) and parameter estimates are shown in Tables 37 and 38, respectively.

The summary statistics for the open-label phase are given in Table 39.

Table 37: CHAQ Score by treatment group by time point

Visit	Adalimumab				Placebo				Total			
	n	missing	Mean (SD)	Median (range)	n	missing	Mean (SD)	Median (range)	n	missing	Mean (SD)	Median (range)
Baseline	59	1	0.52 (0.64)	0.21 (0.00, 2.49)	28	2	0.48 (0.49)	0.45 (0.00, 1.57)	87	3	0.51 (0.59)	0.33 (0.00, 2.49)
1 month	59	1	0.41 (0.56)	0.13 (0.00, 2.29)	30	0	0.60 (0.55)	0.55 (0.00, 1.61)	89	1	0.47 (0.56)	0.22 (0.00, 2.29)
2 months	58	1	0.37 (0.53)	0.11 (0.00, 1.96)	24	1	0.54 (0.59)	0.45 (0.00, 2.32)	82	2	0.42 (0.55)	0.19 (0.00, 2.32)
3 months	55	2	0.35 (0.58)	0.03 (0.00, 2.49)	18	1	0.37 (0.47)	0.19 (0.00, 1.50)	73	3	0.36 (0.55)	0.05 (0.00, 2.49)
6 months	48	4	0.35 (0.59)	0.02 (0.00, 2.49)	12	0	0.46 (0.63)	0.11 (0.00, 2.00)	60	4	0.37 (0.60)	0.05 (0.00, 2.49)
9 months	43	5	0.32 (0.61)	0.04 (0.00, 2.28)	7	0	0.36 (0.57)	0.09 (0.00, 1.58)	50	5	0.33 (0.60)	0.05 (0.00, 2.28)
12 months	43	0	0.29 (0.56)	0.01 (0.00, 2.04)	4	1	0.09 (0.15)	0.02 (0.00, 0.31)	47	1	0.27 (0.54)	0.01 (0.00, 2.04)
15 months	37	1	0.33 (0.51)	0.10 (0.00, 2.00)	3	0	0.03 (0.04)	0.01 (0.00, 0.07)	40	1	0.31 (0.50)	0.08 (0.00, 2.00)
18 months	33	1	0.22 (0.41)	0.01 (0.00, 1.55)	3	0	0.03 (0.05)	0.01 (0.00, 0.09)	36	1	0.21 (0.40)	0.01 (0.00, 1.55)

Table 38: Random intercepts model - CHAQ

Component	Parameter	Estimate	95% Lower	95% Upper	P-value
Longitudinal	(Intercept)	0.20	0.05	0.35	0.01
	Baseline	0.65	0.49	0.76	<0.0001
	Time	-0.01	-0.01	-8e-04	0.01
	Adalimumab	-0.14	-0.32	0.01	0.08
Survival	Adalimumab	-1.42	-2.19	-0.73	0.0001
	HR	0.24	0.11	0.48	0.0001
Association	γ0	0.43	-1.29	1.70	0.54

Table 39: CHAQ Score by treatment group by time point (Open label)

Visit	Adalimumab			
	n	missing	Mean (SD)	Median (range)
Baseline	-	-	-	-
1 month	-	-	-	-
2 months	1	0	0.00 (N/A)	0.00 (0.00, 0.00)
3 months	1	0	0.00 (N/A)	0.00 (0.00, 0.00)
6 months	3	1	0.10 (0.17)	0.00 (0.00, 0.30)
9 months	4	2	0.04 (0.05)	0.02 (0.00, 0.10)
12 months	9	0	0.13 (0.37)	0.01 (0.00, 1.10)
15 months	11	0	0.11 (0.15)	0.00 (0.00, 0.38)
18 months	11	0	0.08 (0.13)	0.01 (0.00, 0.36)

ACR

Summary statistics for ACR are shown in Tables 40-55. Parameter estimates for the integrated analysis of the double blind and open label phase for the adalimumab group and double blind phase for the placebo group are shown in Table 56.

Table 40: ACR Pedi response at 1 month (Integrated Analysis)

ACR Pedi Response	Adalimumab (n (%))	Placebo (n (%))	Total (n (%))
	N=46	N=25	N=71
30	12 (10.9%)	7 (24.1%)	19 (13.7%)
50	7 (8.1%)	7 (25.9%)	14 (12.4%)
70	2 (3.6%)	5 (27.8%)	7 (9.5%)
90	2 (4.4%)	1 (10%)	3 (5.5%)
100	1 (4.8%)	0 (0%)	1 (4.2%)

Table 41: ACR Pedi response at 1 month (Open-label)

ACR Pedi Response	Adalimumab (n (%))
	N=0
30	0 (0%)
50	0 (0%)
70	0 (0%)
90	0 (0%)
100	0 (0%)

Table 42: ACR Pedi response at 2 months (Integrated Analysis)

ACR Pedi Response	Adalimumab (n (%))	Placebo (n (%))	Total (n (%))
	N=45	N=21	N=66
30	16 (14.5%)	8 (27.6%)	24 (17.3%)
50	10 (11.6%)	7 (25.9%)	17 (15%)
70	5 (8.9%)	3 (16.7%)	8 (10.8%)
90	3 (6.7%)	1 (10%)	4 (7.3%)
100	1 (4.8%)	1 (33.3%)	2 (8.3%)

Table 43: ACR Pedi response at 2 months (Open-label)

ACR Pedi Response	Adalimumab (n (%))
	N=0
30	0 (0%)
50	0 (0%)
70	0 (0%)
90	0 (0%)
100	0 (0%)

Table 44: ACR Pedi response at 3 months (Integrated Analysis)

ACR Pedi Response	Adalimumab (n (%))	Placebo (n (%))	Total (n (%))
	N=43	N=16	N=59
30	16 (14.5%)	6 (20.7%)	22 (15.8%)
50	13 (15.1%)	5 (18.5%)	18 (15.9%)
70	9 (16.1%)	3 (16.7%)	12 (16.2%)
90	7 (15.6%)	2 (20%)	9 (16.4%)
100	2 (9.5%)	1 (33.3%)	3 (12.5%)

Table 45: ACR Pedi response at 3 months (Open-label)

ACR Pedi Response	Adalimumab (n (%))
	N=0
30	0 (0%)
50	0 (0%)
70	0 (0%)
90	0 (0%)
100	0 (0%)

Table 46: ACR Pedi response at 6 months (Integrated Analysis)

ACR Pedi Response	Adalimumab (n (%))	Placebo (n (%))	Total (n (%))
	N=39	N=9	N=48
30	14 (12.7%)	3 (10.3%)	17 (12.2%)
50	11 (12.8%)	3 (11.1%)	14 (12.4%)
70	9 (16.1%)	3 (16.7%)	12 (16.2%)
90	6 (13.3%)	2 (20%)	8 (14.5%)
100	2 (9.5%)	1 (33.3%)	3 (12.5%)

Table 47: ACR Pedi response at 6 months (Open-label)

ACR Pedi Response	Adalimumab (n (%))
	N=2
30	1 (7.1%)
50	0 (0%)
70	0 (0%)
90	0 (0%)
100	0 (0%)

Table 48: ACR Pedi response at 9 months (Integrated Analysis)

ACR Pedi Response	Adalimumab (n (%))	Placebo (n (%))	Total (n (%))
	N=37	N=4	N=41
30	12 (10.9%)	1 (3.4%)	13 (9.4%)
50	11 (12.8%)	1 (3.7%)	12 (10.6%)
70	9 (16.1%)	1 (5.6%)	10 (13.5%)
90	8 (17.8%)	1 (10%)	9 (16.4%)
100	5 (23.8%)	0 (0%)	5 (20.8%)

Table 49: ACR Pedi response at 9 months (Open-label)

ACR Pedi Response	Adalimumab (n (%))
	N=5
30	2 (14.3%)
50	2 (16.7%)
70	2 (22.2%)
90	1 (12.5%)
100	0 (0%)

Table 50: ACR Pedi response at 12 months (Integrated Analysis)

ACR Pedi Response	Adalimumab (n (%))	Placebo (n (%))	Total (n (%))
	N=35	N=3	N=38
30	14 (12.7%)	2 (6.9%)	16 (11.5%)
50	12 (14%)	2 (7.4%)	14 (12.4%)
70	7 (12.5%)	1 (5.6%)	8 (10.8%)
90	7 (15.6%)	1 (10%)	8 (14.5%)
100	4 (19%)	0 (0%)	4 (16.7%)

Table 51: ACR Pedi response at 12 months (Open-label)

ACR Pedi Response	Adalimumab (n (%))
	N=7
30	2 (14.3%)
50	2 (16.7%)
70	2 (22.2%)
90	2 (25%)
100	1 (20%)

Table 52: ACR Pedi response at 15 months (Integrated Analysis)

ACR Pedi Response	Adalimumab (n (%))	Placebo (n (%))	Total (n (%))
	N=31	**N=2**	**N=33**
30	11 (10%)	1 (3.4%)	12 (8.6%)
50	9 (10.5%)	1 (3.7%)	10 (8.8%)
70	7 (12.5%)	1 (5.6%)	8 (10.8%)
90	6 (13.3%)	1 (10%)	7 (12.7%)
100	3 (14.3%)	0 (0%)	3 (12.5%)

Table 53: ACR Pedi response at 15 months (Open-label)

ACR Pedi Response	Adalimumab (n (%))
	N=9
30	3 (21.4%)
50	3 (25%)
70	2 (22.2%)
90	2 (25%)
100	2 (40%)

Table 54: ACR Pedi response at 18 months (Integrated Analysis)

ACR Pedi Response	Adalimumab (n (%))	Placebo (n (%))	Total (n (%))
	N=28	**N=2**	**N=30**
30	15 (13.6%)	1 (3.4%)	16 (11.5%)
50	13 (15.1%)	1 (3.7%)	14 (12.4%)
70	8 (14.3%)	1 (5.6%)	9 (12.2%)
90	6 (13.3%)	1 (10%)	7 (12.7%)
100	3 (14.3%)	0 (0%)	3 (12.5%)

Table 55: ACR Pedi response at 18 months (Open-label)

ACR Pedi Response	Adalimumab (n (%))
	N=9
30	6 (42.9%)
50	5 (41.7%)
70	3 (33.3%)
90	3 (37.5%)
100	2 (40%)

Table 56: Parameter Estimates for ACR30, ACR50, ACR70, ACR90 and ACR100

Outcome	Component	Parameter	Estimate	95%Lower	95%Upper	P-value
ACR30	Longitudinal	(Intercept)	-1.35	-2.54	-0.25	0.02
		Time	0.04	-0.01	0.09	0.11
		Adalimumab	0.01	-1.37	1.49	0.99
	Survival	Adalimumab	-1.98	-2.97	-1.07	<0.001
		HR	0.14	0.05	0.34	<0.001
	Association	γ0	-0.21	-0.50	0.03	0.10
ACR50	Longitudinal	(Intercept)	-1.69	-2.97	-0.50	0.01
		Time	0.07	0.01	0.13	0.02
		Adalimumab	-0.71	-2.20	0.78	0.34
	Survival	Adalimumab	-2.12	-3.15	-1.24	<0.001
		HR	0.12	0.04	0.29	<0.001
	Association	γ0	-0.26	-0.58	-0.02	0.04
ACR70	Longitudinal	(Intercept)	-2.72	-4.10	-1.54	<0.001
		Time	0.08	0.01	0.14	0.02
		Adalimumab	-1.11	-2.68	0.42	0.16
	Survival	Adalimumab	-2.34	-4.06	-1.18	<0.001
		HR	0.10	0.02	0.31	<0.001
	Association	γ0	-0.38	-0.99	-0.04	0.02
ACR90	Longitudinal	(Intercept)	-4.74	-6.48	-3.20	<0.001
		Time	0.11	0.04	0.18	0.004
		Adalimumab	-0.48	-2.47	1.44	0.62
	Survival	Adalimumab	-2.55	-4.21	-1.30	<0.001
		HR	0.08	0.01	0.27	<0.001
	Association	γ_0	-0.38	-0.85	-0.07	0.01
ACR100	Longitudinal	(Intercept)	-5.13	-6.38	-3.92	<0.001
		Time	0.10	0.01	0.18	0.03
		Adalimumab	-0.43	-1.91	1.04	0.57
	Survival	Adalimumab	-2.37	-4.52	-1.15	<0.001
		HR	0.09	0.01	0.32	<0.001
	Association	γ0	-0.44	-1.18	0.15	0.18

Number of participants undergoing disease flares

There were no further events of disease flares within the open label phase, therefore, no integrated analysis of the double blind and open label data was conducted.

Number of participants in remission on medication for their JIA

Seven participants (11.7%) in the adalimumab group and 17 (56.7%) participants in the placebo group could not be included in the analysis due to the fact that they had not been on medication for the required amount of time (six months) in the definition of the outcome (Table 1).

The risk of having remission on medication in the adalimumab group was greater than that on placebo but was not statistically significant (Table 1).

Three patients had remission on medication for their JIA during the open label phase (Table 58).

Table 57: Number of participants in remission on medication for their JIA (for 6 months)

		Adalimumab	Placebo	Total	RR 95% CI	p-value
Analysis status	**N**	60	30	90	-	-
	Excluded	7 (11.7%)	17 (56.7%)	24 (26.7%)	-	-
	Included	53 (88.3%)	13 (43.3%)	66 (73.3%)	-	-
Achieved event	**N**	53	13	66	5.40 (0.30,87.40)	0.19
	No	43 (81.1%)	13 (100%)	56 (84.8%)		
	Yes	10 (18.9%)	0 (0%)	10 (15.2%)		

Table 58: Line listing of participants who achieved remission on medication for their JIA for 6 months in the open-label phase

Participant	Date of randomisation	Date of unblinding	Period of remission achieved	Visit from	Visit to
0243089	10/2/2015	6/5/2015	8/4/2015-21/10/2015	Treatment Visit 2 - 2 Months Treatment	Treatment Visit 5 - 9 Months Treatment
0249083	5/12/2014	22/5/2015	22/5/2015-6/11/2015	Treatment Visit 4 - 6 Months Treatment	Treatment Visit 6 - 12 Months Treatment
0116088	5/2/2015	30/4/2015	7/1/2016-23/6/2016	Treatment Visit 6 - 12 Months Treatment	End of Treatment Visit 8 - 18 Months Treatment

Number of participants in remission off medication for their JIA

An integrated analysis of the blinded phase and open-label phase was planned, however, no participants in either the adalimumab group or the placebo group achieved remission off medication for their JIA and therefore the analysis was not possible.

Number of participants with minimum disease activity

The data are presented for the integrated analysis of the double blind and open label phase for the adalimumab group and the double blind phase for the placebo group.

During the open label phase there were three patients on adalimumab who had minimum disease activity.

The number of participants with minimum disease activity at each time point is reported in **Error! eference source not found.**. There was a total of 22 (37.29%) participants in the adalimumab group who had at least one case of minimum disease activity during the course of the trial and 4 participants in the placebo group (**Error! Reference source not found.**). The RR 95% CI was 2.70 1.03, 7.12) and the associated p-value from the chi-squared test was 0.03, indicating that there was a statistically significant difference between the two groups.

Number of participants requiring change in biologic and/or DMARD therapy for arthritis due to failure to respond

There were no further events of change in biologic/DMARD therapy within the open label phase, therefore, no integrated analysis of the double blind and open label data was conducted.

Participants score of the Juvenile Arthritis Disease Activity Score

Tables 59-61 show the summary statistics and tables 62-64 show the parameter estimates from the integrated analysis of the double blind and open label phase for the adalimumab group and the double blind phase for the placebo group.

Tables 65-67 show the summary statistics from the open-label phase only.

Table 59: JADAS10

Visit	Adalimumab									Placebo								
	N	Missing	Mean	SD	Median	Lower quartile	Upper quartile	Min	Max	N	Missing	Mean	SD	Median	Lower quartile	Upper quartile	Min	Max
Baseline	44	16	3.48	4.2	1.9	0.4	4.7	0	17.3	22	8	4.15	5.61	1.55	0.9	5.3	0	23.8
1 month	37	23	2.03	2.31	1.4	0.3	2.5	0	11	17	13	3.12	3.84	1.8	0.3	4.1	0	13.6
2 months	46	13	1.62	2.29	0.65	0.1	2.2	0	11.1	17	8	3.72	5.76	2	0.2	5	0	23.5
3 months	40	17	1.54	2.13	0.65	0.15	1.85	0	8.7	13	6	3.56	4.64	1.2	0.2	6	0.1	13.8
6 months	39	13	1.69	2.41	0.3	0	3.5	0	7.3	10	2	3.02	3.8	1	0.2	4	0	9.8
9 months	32	16	1.02	1.44	0.45	0.05	1.45	0	5	5	2	1.42	1.24	1.9	0.2	1.9	0.1	3
12 months	30	13	1.22	2.2	0.25	0	1.4	0	9.6	3	2	0.2	0.26	0.1	0	0.5	0	0.5
15 months	25	13	1.25	2.01	0.3	0.1	2	0	9	3	0	1.33	0.97	1.1	0.5	2.4	0.5	2.4
18 months	22	12	1.23	1.64	0.6	0.1	1.4	0	5.4	3	0	1.5	1.31	0.9	0.6	3	0.6	3

Table 60: JADAS27

Visit	Adalimumab									Placebo								
	N	Missing	Mean	SD	Median	Lower quartile	Upper quartile	Min	Max	N	Missing	Mean	SD	Median	Lower quartile	Upper quartile	Min	Max
Baseline	44	16	3.29	3.89	1.9	0.4	4.7	0	18.4	22	8	3.65	4.41	1.55	0.9	4.8	0	16.8
1 month	37	23	1.92	1.94	1.4	0.3	2.5	0	7	17	13	2.59	2.71	1.8	0.3	4.1	0	8.5
2 months	46	13	1.62	2.29	0.65	0.1	2.2	0	11.1	17	8	3.43	5.4	2	0.2	5	0	22.5
3 months	40	17	1.49	1.97	0.65	0.15	1.85	0	8	13	6	3.25	4.04	1.2	0.2	6	0.1	11.8
6 months	39	13	1.64	2.31	0.3	0	3.5	0	7.3	10	2	3.02	3.8	1	0.2	4	0	9.8
9 months	32	16	1.02	1.44	0.45	0.05	1.45	0	5	5	2	1.42	1.24	1.9	0.2	1.9	0.1	3
12 months	30	13	1.22	2.2	0.25	0	1.4	0	9.6	3	2	0.2	0.26	0.1	0	0.5	0	0.5
15 months	25	13	1.21	1.99	0.3	0.1	1.5	0	9	3	0	1.33	0.97	1.1	0.5	2.4	0.5	2.4
18 months	22	12	1.23	1.64	0.6	0.1	1.4	0	5.4	3	0	1.5	1.31	0.9	0.6	3	0.6	3

Table 61: JADAS71

Visit	Adalimumab									Placebo								
	N	Missing	Mean	SD	Median	Lower quartile	Upper quartile	Min	Max	N	Missing	Mean	SD	Median	Lower quartile	Upper quartile	Min	Max
Baseline	44	16	3.54	4.43	1.9	0.4	4.7	0	19.4	22	8	4.24	5.95	1.55	0.9	5.3	0	25.8
1 month	37	23	2.03	2.31	1.4	0.3	2.5	0	11	17	13	3.29	4.38	1.8	0.3	4.1	0	16.6
2 months	46	13	1.62	2.29	0.65	0.1	2.2	0	11.1	17	8	3.72	5.76	2	0.2	5	0	23.5
3 months	40	17	1.54	2.13	0.65	0.15	1.85	0	8.7	13	6	3.79	5.23	1.2	0.2	6	0.1	16.8
6 months	39	13	1.69	2.41	0.3	0	3.5	0	7.3	10	2	3.02	3.8	1	0.2	4	0	9.8
9 months	32	16	1.02	1.44	0.45	0.05	1.45	0	5	5	2	1.42	1.24	1.9	0.2	1.9	0.1	3
12 months	30	13	1.22	2.2	0.25	0	1.4	0	9.6	3	2	0.2	0.26	0.1	0	0.5	0	0.5
15 months	25	13	1.25	2.01	0.3	0.1	2	0	9	3	0	1.33	0.97	1.1	0.5	2.4	0.5	2.4
18 months	22	12	1.23	1.64	0.6	0.1	1.4	0	5.4	3	0	1.5	1.31	0.9	0.6	3	0.6	3

Table 62: Parameter estimates from joint modelling (random-intercepts only) for JADAS10

Component	Parameter	Estimate	95% Lower	95% Upper	P-value
Longitudinal	(Intercept)	0.61	0.22	1.07	0.004
	Baseline	0.43	0.24	0.57	<0.0001
	Time	-0.01	-0.02	0.01	0.26
	Adalimumab	-0.35	-0.76	0.02	0.08
Survival	Adalimumab	-2.25	-3.65	-1.37	0.15
	HR	0.11	0.03	0.25	0.15
Association	γ0	1.07	-0.02	2.56	0.09

Table 63: Parameter estimates from joint modelling (random-intercepts only) for JADAS27

Component	Parameter	Estimate	95% Lower	95% Upper	P-value
Longitudinal	(Intercept)	0.60	0.21	1.04	0.003
	Baseline	0.42	0.24	0.57	<0.0001
	Time	-0.01	-0.02	0.01	0.28
	Adalimumab	-0.33	-0.75	0.04	0.09
Survival	Adalimumab	-2.24	-3.67	-1.35	0.15
	HR	0.11	0.03	0.26	0.15
Association	γ0	1.05	-0.01	2.54	0.09

Table 64: Parameter estimates from joint modelling (random-intercepts only) for JADAS71

Component	Parameter	Estimate	95% Lower	95% Upper	P-value
Longitudinal	(Intercept)	0.62	0.22	1.08	0.004
	Baseline	0.43	0.24	0.57	<0.0001
	Time	-0.01	-0.02	0.01	0.26
	Adalimumab	-0.35	-0.77	0.01	0.07
Survival	Adalimumab	-2.25	-3.63	-1.37	0.15
	HR	0.11	0.03	0.25	0.15
Association	γ0	1.07	-0.03	2.49	0.09

Table 65: JADAS10 Summary Statistics for open-label phase

	Adalimumab								
Visit	**N**	**Missing**	**Mean**	**SD**	**Median**	**Lower quartile**	**Upper quartile**	**Min**	**Max**
Baseline	0	0	.	.	.	.	.	.	.
1 month	0	0	.	.	.	.	.	.	.
2 months	0	1	.	.	.	.	.	.	.
3 months	0	1	.	.	.	.	.	.	.
6 months	2	2	0	0	0	0	0	0	0
9 months	4	3	0.3	0.29	0.3	0.05	0.55	0	0.6
12 months	5	5	0.06	0.09	0	0	0.1	0	0.2
15 months	5	9	1.98	3.93	0.1	0.1	0.7	0	9
18 months	9	5	0.68	0.91	0.2	0.1	0.9	0	2.8

Table 66: JADAS27 Summary Statistics for the open-label phase

	Adalimumab								
Visit	**N**	**Missing**	**Mean**	**SD**	**Median**	**Lower quartile**	**Upper quartile**	**Min**	**Max**
Baseline	0	0	.	.	.	.	.	.	.
1 month	0	0	.	.	.	.	.	.	.
2 months	0	1	.	.	.	.	.	.	.
3 months	0	1	.	.	.	.	.	.	.
6 months	2	2	0	0	0	0	0	0	0
9 months	4	3	0.3	0.29	0.3	0.05	0.55	0	0.6
12 months	5	5	0.06	0.09	0	0	0.1	0	0.2
15 months	5	9	1.98	3.93	0.1	0.1	0.7	0	9
18 months	9	5	0.68	0.91	0.2	0.1	0.9	0	2.8

Table 67: JADAS71 Summary Statistics for the open-label phase

	Adalimumab								
Visit	**N**	**Missing**	**Mean**	**SD**	**Median**	**Lower quartile**	**Upper quartile**	**Min**	**Max**
Baseline	0	0	.	.	.	.	.	.	.
1 month	0	0	.	.	.	.	.	.	.
2 months	0	1	.	.	.	.	.	.	.
3 months	0	1	.	.	.	.	.	.	.
6 months	2	2	0	0	0	0	0	0	0
9 months	4	3	0.3	0.29	0.3	0.05	0.55	0	0.6
12 months	5	5	0.06	0.09	0	0	0.1	0	0.2
15 months	5	9	1.98	3.93	0.1	0.1	0.7	0	9
18 months	9	5	0.68	0.91	0.2	0.1	0.9	0	2.8

Treatment Compliance

Treatment compliance was measured using both patient completed diaries and also accountability logs. The accountability logs documented the number of vials that were issued to a patient and also the number of vials that were returned either used or unused. If a patient failed to return a vial then this was considered to be missing.

Compliance was evaluated at each treatment visit by the research team.

Treatment compliance (%) for adalimumab and placebo based on the patient report diary was defined as the number of study drug doses recorded as being taken divided by the expected number of drug doses (based on when they started taking their study drug). Treatment compliance (%) based on the accountability logs was calculated as the number of vials returned used (missing vials were assumed to be used) divided by the number of vials issued.

Analysis of the integrated treatment compliance data from the double blind phase and the open label phase for the adalimumab group was 83.29% and 93.85% according to the patient diaries and accountability logs, respectively.

Laboratory parameters

Haematological

Table 68 gives the mean difference (standard error) of change in haematological laboratory parameters from baseline to each treatment visit for the integrated analysis of the double blind and open label data for the adalimumab group and the double blind phase for the placebo group. Differences marked by an asterisk were significant at the 5% level. None of the mean changes in haematological assessments were considered to be clinically significant.

Table 68: Mean difference in haematological variables from baseline to each treatment visit of adalimumab compared to placebo

Variable	Mean difference of change from baseline in adalimumab compared to placebo (Standard Error)							
	1 month	2 months	3 months	6 months	9 months	12 months	15 months	18 months
Haematocrit (%)	0.44 (0.60)	0.28 (0.56)	-0.74 (0.67)	-1.17 (0.74)	-0.75 (1.17)	-1.63 (1.43)	0.07 (1.55)	1.24 (1.64)
Haemoglobin (g/dL)	0.08 (0.17)	0.02 (0.17)	-0.13 (0.18)	-0.39 (0.24)	-0.33 (0.35)	-0.43 (0.40)	-0.33 (0.56)	0.40 (2.09)
Red blood cell count (10^{12}/L)	0.00 (0.06)	0.00 (0.06)	-0.07 (0.06)	-0.20 (0.08)*	-0.17 (0.11)	-0.14 (0.13)	-0.25 (0.14)	-0.18 (0.16)
White blood cell count (10^{12}/L)	0.33 (0.53)	0.06 (0.65)	-0.26 (1.16)	1.10 (0.68)	0.06 (0.94)	1.05 (1.32)	1.48 (1.33)	0.58 (1.44)
Neutrophils (10^9/L)	-0.07 (0.45)	-0.65 (0.52)	-0.83 (1.09)	0.56 (0.57)	-0.52 (0.68)	0.18 (0.96)	0.46 (1.06)	-0.20 (1.19)
Lymphocytes (10^9/L)	0.39 (0.15)*	0.48 (0.21)*	0.38 (0.24)	0.35 (0.21)	0.60 (0.37)	0.75 (0.41)	0.65 (0.58)	0.45 (0.35)
Monocytes (10^9/L)	0.04 (0.04)	0.07 (0.05)	0.07 (0.06)	0.11 (0.06)	0.09 (0.08)	0.12 (0.10)	0.24 (0.13)	0.11 (0.11)
Basophils (10^9/L)	0.01 (0.01)	0.00 (0.01)	-0.00 (0.01)	-0.00 (0.01)	-0.01 (0.01)	-0.00 (0.01)	0.01 (0.01)	-0.01 (0.01)
Eosinophils (10^9/L)	0.04 (0.06)	0.07 (0.05)	0.14 (0.05)*	0.11 (0.08)	-0.01 (0.06)	-0.04 (0.24)	0.08 (0.12)	0.17 (0.12)
Platelet count (10^9/L)	-3.34 (12.80)	-9.63 (12.27)	-27.01 (15.99)	-21.34 (17.10)	-19.55 (21.36)	-4.62 (31.89)	-14.17 (34.59)	-24.02 (38.00)
ESR	0.09 (3.49)	-1.77 (3.01)	-1.35 (3.21)	-3.36 (4.96)	-2.81 (3.24)	2.93 (4.90)	0.29 (7.07)	4.26 (7.00)
Plasma viscosity**	NA	NA	NA	NA	NA	NA	NA	NA

**In the placebo arm there was only 1 assessment done at baseline and months 1, 2, 3 and 6, none were done at months 9, 12, 15 and 18 and therefore no mean difference could be calculated between the two groups.

Tables 69-80 show the haematological summary data from the open-label phase.

Table 69: Haematocrit Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	1 (100.00%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	5 (71.43%)	1 (14.29%)	1 (100.00%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	8 (88.89%)	1 (11.11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	8 (72.73%)	2 (18.18%)	0 (0%)	0 (0%)	1 (9.09%)	0 (0%)
18 months	11	8 (72.73%)	3 (27.27%)	1 (33.33%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 70: Haemoglobin Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	1 (100.00%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	5 (71.43%)	1 (14.29%)	0 (0%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	8 (88.89%)	1 (11.11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	10 (90.91%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	8 (72.73%)	3 (27.27%)	2 (66.67%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 71: Red blood cell count Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	0 (0%)	0 (0%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	8 (88.89%)	1 (11.11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	10 (90.91%)	1 (9.09%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 72: White blood cell count Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	0 (0%)	0 (0%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	7 (77.78%)	2 (22.22%)	1 (50.00%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 73: Neutrophils Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	0 (0%)	0 (0%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	8 (88.89%)	1 (11.11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	10 (90.91%)	1 (9.09%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 74: Lymphocytes Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	1 (100.00%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	0 (0%)	0 (0%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	9 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 75: Monocytes Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	0 (0%)	0 (0%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	9 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	10 (90.91%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 76: Basophils Assessments (open label)– Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	0 (0%)	0 (0%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	9 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 77: Eosinophils Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	0 (0%)	0 (0%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	8 (88.89%)	1 (11.11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	9 (81.82%)	2 (18.18%)	2 (100.00%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 78: Platelet count Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	1 (100.00%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	3 (75.00%)	1 (25.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	0 (0%)	0 (0%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	8 (88.89%)	1 (11.11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	10 (90.91%)	1 (9.09%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	10 (90.91%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 79: Erythrocyte sedimentation rate Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	1 (100.00%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	0 (0%)	0 (0%)	0 (0%)	1 (14.29%)	0 (0%)
12 months	9	6 (66.67%)	1 (11.11%)	0 (0%)	0 (0%)	2 (22.22%)	0 (0%)
15 months	11	6 (54.55%)	2 (18.18%)	2 (100.00%)	1 (50.00%)	3 (27.27%)	0 (0%)
18 months	11	7 (63.64%)	2 (18.18%)	2 (100.00%)	0 (0%)	2 (18.18%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 80: Plasma viscosity Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.00%)
3 months	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.00%)
6 months	4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (100.00%)
9 months	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (100.00%)
12 months	9	2 (22.22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (77.78%)
15 months	11	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	2 (18.18%)	8 (72.73%)
18 months	11	2 (18.18%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (81.82%)

*Assessment missing but not recorded as 'Not done' on CRF

Biochemical

Table 81 gives the mean difference (standard error) of change in biochemical laboratory parameters from baseline to each treatment visit for the integrated analysis of the double blind and open label data for the adalimumab group and the double blind phase for the placebo group. Differences marked by an asterisk were significant at the 5% level. None of the mean changes in biochemical assessments were considered to be clinically significant.

Table 81: Mean difference (standard error) in biochemical variables from baseline to each treatment visit of adalimumab compared to placebo

Variable	1 month	2 months	3 months	6 months	9 months	12 months	15 months	18 months
CRP (mg/L)	1.15 (2.43)	0.24 (1.42)	0.05 (3.06)	-1.12 (1.72)	-1.97 (2.04)	-0.29 (1.99)	2.97 (7.80)	3.87 (10.49)
Urea (mmol/L)	-0.43 (0.21)*	-0.58 (0.25)*	-0.59 (0.27)*	-0.35 (0.38)	-0.70 (0.49)	-1.04 (0.55)	-1.59 (0.79)	-1.44 (0.71)
Creatinine (mmol/L)	-1.19 (1.86)	-2.26 (2.25)	0.56 (2.27)	0.22 (1.88)	-1.14 (4.98)	-0.08 (3.01)	-0.83 (3.78)	-22.74 (7.20)*
Sodium (mmol/L)	1.07 (0.61)	1.16 (0.64)	-0.03 (0.54)	0.18 (0.93)	0.00 (1.12)	0.43 (1.18)	-0.56 (1.73)	0.28 (1.73)
Potassium (mmol/L)	-0.05 (0.10)	0.01 (0.11)	0.00 (0.13)	-0.28 (0.14)	0.14 (0.31)	0.17 (0.29)	0.05 (0.21)	-0.14 (0.19)
Calcium (mmol/L)	0.02 (0.02)	0.01 (0.03)	0.04 (0.03)	0.01 (0.03)	-0.01 (0.05)	0.04 (0.05)	0.02 (0.05)	-0.06 (0.07)
Inorganic phosphate (mmol/L)	0.05 (0.06)	0.04 (0.06)	-0.03 (0.06)	0.02 (0.07)	0.09 (0.12)	-0.07 (0.12)	-0.06 (0.14)	-0.08 (0.17)
Glucose (mmol/L)	-0.06 (0.30)	-0.33 (0.30)	0.14 (0.30)	0.46 (0.40)	0.16 (0.72)	0.02 (0.74)	0.71 (0.78)	0.03 (0.79)
Chloride (mmol/L)	0.86 (0.63)	0.31 (0.68)	1.18 (0.75)	1.29 (0.93)	0.74 (1.25)	0.77 (1.28)	-0.65 (1.83)	-0.07 (1.78)
Bicarbonate (mmol/L)	0.28 (1.08)	-0.41 (1.00)	-1.34 (1.01)	-0.03 (1.50)	-3.69 (2.51)	1.50 (2.16)	0.69 (3.13)	0.04 (2.47)
Total bilirubin (mmol/L)	1.08 (0.89)	1.26 (0.92)	-0.36 (0.95)	0.64 (1.48)	1.79 (1.83)	2.95 (2.45)	0.17 (3.20)	-3.35 (2.32)
ALT (iu/L)	2.67 (8.05)	3.22 (9.00)	-4.18 (8.22)	-2.03 (11.85)	19.29 (40.43)	1.38 (10.09)	10.29 (18.46)	1.81 (12.23)
AST (iu/L)	-3.32 (2.47)	-3.63 (2.72)	-1.07 (4.26)	-4.01 (4.84)	5.83 (24.41)	-11.89 (6.89)	-11.89 (13.45)	5.92 (12.46)

Tables 82-94 show the biochemical data from the open-label phase.

Table 82: C-Reactive Protein Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	**Normal assessments, N (%)**	**Abnormal assessments, N (%)**	**If abnormal, number expected, N (%)**	**If abnormal, number of clinically significant, N (%)**	**Assessment recorded as not done, N (%)**	**Missing*, N (%)**
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	1 (14.29%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	7 (77.78%)	2 (22.22%)	2 (100.00%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	7 (63.64%)	3 (27.27%)	3 (100.00%)	1 (33.33%)	1 (9.09%)	0 (0%)
18 months	11	10 (90.91%)	1 (9.09%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 83: Urea Assessments (open label) – Adalimumab

Time point	**Adalimumab**						
	Number of assessments, N	**Normal assessments, N (%)**	**Abnormal assessments, N (%)**	**If abnormal, number expected, N (%)**	**If abnormal, number of clinically significant, N (%)**	**Assessment recorded as not done, N (%)**	**Missing*, N (%)**
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	2 (50.00%)	2 (50.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	1 (14.29%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	8 (88.89%)	1 (11.11%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	9 (81.82%)	2 (18.18%)	2 (100.00%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 84: Creatinine Assessments (open label) – Adalimumab

Time point	**Adalimumab**						
	Number of assessments, N	**Normal assessments, N (%)**	**Abnormal assessments, N (%)**	**If abnormal, number expected, N (%)**	**If abnormal, number of clinically significant, N (%)**	**Assessment recorded as not done, N (%)**	**Missing*, N (%)**
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	1 (14.29%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	8 (88.89%)	1 (11.11%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	10 (90.91%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	10 (90.91%)	1 (9.09%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 85: Sodium Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	7 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	9 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 86: Potassium Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	7 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	9 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	10 (90.91%)	1 (9.09%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	10 (90.91%)	1 (9.09%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 87: Calcium Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	7 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	8 (88.89%)	0 (0%)	0 (0%)	0 (0%)	1 (11.11%)	0 (0%)
15 months	11	10 (90.91%)	0 (0%)	0 (0%)	0 (0%)	1 (9.09%)	0 (0%)
18 months	11	10 (90.91%)	0 (0%)	0 (0%)	0 (0%)	1 (9.09%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 88: Inorganic phosphate Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	6 (85.71%)	1 (14.29%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	7 (77.78%)	1 (11.11%)	0 (0%)	0 (0%)	1 (11.11%)	0 (0%)
15 months	11	8 (72.73%)	2 (18.18%)	1 (50.00%)	0 (0%)	1 (9.09%)	0 (0%)
18 months	11	10 (90.91%)	0 (0%)	0 (0%)	0 (0%)	1 (9.09%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 89: Glucose Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	0 (0%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	7 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	7 (77.78%)	1 (11.11%)	0 (0%)	0 (0%)	1 (11.11%)	0 (0%)
15 months	11	8 (72.73%)	2 (18.18%)	1 (50.00%)	0 (0%)	1 (9.09%)	0 (0%)
18 months	11	9 (81.82%)	0 (0%)	0 (0%)	0 (0%)	2 (18.18%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 90: Chloride Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.00%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	7 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	9 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	10 (90.91%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 91: Bicarbonate Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.00%)	0 (0%)
3 months	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.00%)	0 (0%)
6 months	4	3 (75.00%)	0 (0%)	0 (0%)	0 (0%)	1 (25.00%)	0 (0%)
9 months	7	4 (57.14%)	1 (14.29%)	0 (0%)	0 (0%)	2 (28.57%)	0 (0%)
12 months	9	5 (55.56%)	3 (33.33%)	1 (33.33%)	0 (0%)	1 (11.11%)	0 (0%)
15 months	11	6 (54.55%)	3 (27.27%)	1 (33.33%)	0 (0%)	2 (18.18%)	0 (0%)
18 months	11	7 (63.64%)	2 (18.18%)	1 (50.00%)	0 (0%)	2 (18.18%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 92: Total bilirubin Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	4 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9 months	7	7 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	9 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	11 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 93: Alanine aminotransferase Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	1 (100.00%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
3 months	1	0 (0%)	1 (100.00%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	3 (75.00%)	1 (25.00%)	0 (0%)	1 (100.00%)	0 (0%)	0 (0%)
9 months	7	5 (71.43%)	2 (28.57%)	1 (50.00%)	0 (0%)	0 (0%)	0 (0%)
12 months	9	7 (77.78%)	2 (22.22%)	1 (50.00%)	0 (0%)	0 (0%)	0 (0%)
15 months	11	9 (81.82%)	2 (18.18%)	1 (50.00%)	0 (0%)	0 (0%)	0 (0%)
18 months	11	10 (90.91%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Assessment missing but not recorded as 'Not done' on CRF

Table 94: Aspartate aminotransferase Assessments (open label) – Adalimumab

Time point	Adalimumab						
	Number of assessments, N	Normal assessments, N (%)	Abnormal assessments, N (%)	If abnormal, number expected, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not done, N (%)	Missing*, N (%)
Baseline	0	NA	NA	NA	NA	NA	NA
1 month	0	NA	NA	NA	NA	NA	NA
2 months	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.00%)	0 (0%)
3 months	1	0 (0%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months	4	2 (50.00%)	1 (25.00%)	0 (0%)	1 (100.00%)	1 (25.00%)	0 (0%)
9 months	7	4 (57.14%)	2 (28.57%)	0 (0%)	1 (50.00%)	1 (14.29%)	0 (0%)
12 months	9	7 (77.78%)	1 (11.11%)	1 (100.00%)	0 (0%)	1 (11.11%)	0 (0%)
15 months	11	8 (72.73%)	2 (18.18%)	1 (50.00%)	0 (0%)	1 (9.09%)	0 (0%)
18 months	11	9 (81.82%)	0 (0%)	0 (0%)	0 (0%)	2 (18.18%)	0 (0%)

Urinalysis

Table 95 shows the number of abnormal urinalysis assessments in each treatment group over time. Details on the microscopic analysis are presented in Table 29. Overall the results from the urinalysis were not clinically significant.

Table 95: Number of abnormal urinalysis assessments at each visit

Visit	Allocation	Number of abnormal assessments (number of participants)
Baseline	Adalimumab	19 (17)
	Placebo	15 (13)
Month 1	Adalimumab	20 (15)
	Placebo	12 (8)
Month 2	Adalimumab	23 (18)
	Placebo	9 (7)
Month 3	Adalimumab	15 (13)
	Placebo	9 (7)
Month 6	Adalimumab	18 (12)
	Placebo	4 (4)
Month 9	Adalimumab	15 (12)
	Placebo	5 (4)
Month 12	Adalimumab	13 (12)
	Placebo	4 (3)
Month 15	Adalimumab	9 (9)
	Placebo	1 (1)
Month 18	Adalimumab	10 (9)
	Placebo	1 (1)

Table 96: Microscopic Urinalysis results

Time point	Allocation	Number of assessments, N	Normal assessments, N (%)	Abnormal Assessment, N (%)	If abnormal, number of clinically significant, N (%)	Assessment recorded as not applicable, N (%)	Missing*, N (%)
Baseline	Adalimumab	17	9 (52.94%)	7 (41.18%)	1 (14.29%)	1 (5.88%)	0 (0%)
	Placebo	13	7 (53.85%)	4 (30.77%)	0 (0%)	2 (15.38%)	0 (0%)
1 month	Adalimumab	15	8 (53.33%)	3 (20.00%)	0 (0%)	4 (26.67%)	0 (0%)
	Placebo	8	4 (50.00%)	3 (37.50%)	0 (0%)	1 (12.50%)	0 (0%)
2 months	Adalimumab	18	11 (61.11%)	3 (16.67%)	1 (33.33%)	3 (16.67%)	1 (5.56%)
	Placebo	7	3 (42.86%)	3 (42.86%)	0 (0%)	0 (0%)	1 (14.29%)
3 months	Adalimumab	13	9 (69.23%)	3 (23.08%)	0 (0%)	1 (7.69%)	0 (0%)
	Placebo	7	4 (57.14%)	2 (28.57%)	0 (0%)	0 (0%)	1 (14.29%)
6 months	Adalimumab	12	6 (50.00%)	4 (33.33%)	2 (50.00%)	2 (16.67%)	0 (0%)
	Placebo	4	4 (100.00%)	0 (0%)	N/A	0 (0%)	0 (0%)
9 months	Adalimumab	12	6 (50.00%)	6 (50.00%)	2 (33.33%)	0 (0%)	0 (0%)
	Placebo	4	3 (75.00%)	0 (0%)	N/A	0 (0%)	1 (25.00%)
12 months	Adalimumab	12	7 (58.33%)	4 (33.33%)	3 (75.00%)	1 (8.33%)	0 (0%)
	Placebo	3	1 (33.33%)	2 (66.67%)	0 (0%)	0 (0%)	0 (0%)
15 months	Adalimumab	9	5 (55.56%)	3 (33.33%)	0 (0%)	1 (11.11%)	0 (0%)
	Placebo	1	0 (0%)	0 (0%)	N/A	1 (100.00%)	0 (0%)
18 months	Adalimumab	8	3 (37.50%)	3 (37.50%)	2 (66.67%)	2 (25.00%)	0 (0%)
	Placebo	1	0 (0%)	1 (100.00%)	0 (0%)	0 (0%)	0 (0%)