Teriflunomide (Aubagio) for the treatment of relapsing remitting multiple sclerosis

ERG commentary on the additional information submitted by the manufacturer in response to the ACD

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Section 1: Introduction

The ERG was requested by NICE to provide validity checks on the additional evidence submitted by the manufacturer in response to the ACD and to identify any areas of remaining uncertainty. Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the manufacturer's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG has checked the implementation of any proposed changes and ensured replication of the results presented by the manufacturer. In addition, the ERG has also undertaken additional scenario analysis to address remaining issues or areas of uncertainty that it considered were not reflected in the manufacturer's response.

The manufacturer's response to the ACD included:

1. A mixed treatment comparison adjusting for baseline ARR
2. An amended version of the economic model (also incorporating the results of the adjusted MTC);
3. A revised base case using the preferred assumptions outlined by the Appraisal Committee;
4. A sensitivity analysis incorporating direct non-medical costs;
5. A sensitivity analysis exploring different treatment sequences;
6. A validation comparing the manufacturer's model to a previous technology appraisal and observational data.

The ERG considers that the documentation submitted by the manufacturer largely reflects amendments and corrections intended to address the committee's considerations raised within the ACD, as opposed to being based on new data related to teriflunomide. The new evidence submitted by the manufacturer specifically relates to the mixed treatment comparison recommended by the ERG and requested by the committee and which is now used in the economic model to inform treatment effects on disease progression, annual relapse rate and withdrawal. The remainder of the changes proposed within the revised base-case all relate to the same evidence previously critiqued by the ERG in the main evaluation report. Consequently, the ERG views of these issues remain largely unaltered.

Section 2: Review of the mixed treatment comparison adjusted for baseline annual relapse rate

The meta-regression methods are acceptable. A more complex model that would have allowed inclusion of all trials would have been preferable but the rationale for the simpler model (i.e. that the data were too sparse) is reasonable. The impact of the meta-regression on the results is derived to a large extent from the fact that the trials with the highest baseline relapse rates included the only placebo comparisons of Rebif 44 and of Betaferon and also one of the GA placebo controlled trials (Bornstein, 1987, GA vs. placebo, 2.58; IFNB study group, IFNB-250 vs. placebo, 2.30; PRISMS, Rebif vs. placebo, 2.01). The interaction between baseline relapse rate and ARR is small and not significant, but those for 3 month SAD and discontinuations are larger and significant. Thus in the meta-regression the effect sizes of these three drugs for 3 month SAD and discontinuations are downgraded.

The results generated by the adjusted All years MTC analysis are in the most part very similar to the original base case and All Years results. For ARR the results are very similar to the Base Case and All Years analyses but the comparisons of teriflunomide with the other active agents do favour teriflunomide slightly more than did the original analyses. Interestingly for the outcome ARR the result for the comparison of teriflunomide 14 mg with Rebif 44µg from the Adjusted All years analysis was also inconsistent with the direct evidence where neither the Base case and All Years analysis had been (Table 1). The result for the comparison between teriflunomide and GA is between those from the Base Case and All Years network.

The main concerns with the original MTC were the inconsistency between the MTC results for 3 months SAD and the direct trial results for the comparison of Betaferon 250µg with placebo and teriflunomide with Rebif 44 (TENERE), particularly in the Base Case network. For the comparison of Betaferon 250µg with placebo the trial result of [redacted] non-significant treatment disbenefit in the base case analysis. The result from the All Years adjusted for baseline relapse rate analysis was similar to that from the All years network but still somewhat inconsistent with the direct result (Table 2) though [redacted] The comparison between teriflunomide and GA is the same as for the Base case analysis, but with narrower confidence intervals: this is more favourable to teriflunomide than the All years analysis result.

Interestingly, the quite large differences between the direct and base case MTC results seen for the comparison of teriflunomide 14 mg with Rebif 44µg for the 3month SAD outcome were even greater from the Adjusted All years analysis (Table 2). This result is important as this outcome is the key driver in the model this reduction in HR has a notable impact on the results of the cost-effectiveness analysis.

Similarly for the outcome discontinuations the result for the comparison of teriflunomide 14 mg with Rebif 44µg from the Adjusted All years analysis was more inconsistent with the direct evidence than both the Base case and All Years analysis (Table 3). However, for other comparisons where direct evidence is available the Adjusted All years analysis of discontinuations are more consistent than the other two analyses. Again the comparison between teriflunomide and GA is similar to the Base case analysis result, but with narrower confidence intervals: this is more favourable to teriflunomide than the All years analysis result.

Table 1: MTC results ARR

	Base case analysis	All Years analysis	Adjusted All Years analysis	Direct results available*
Comparison	**Rate ratio [95% CrI]**	**Rate Ratio [95% CrI]**	**Rate Ratio [95% CrI]**	
Teriflunomide 14mg vs. Placebo	0.67 [0.57, 0.77]	[redacted]	[redacted]	O'Connor P, 2006: 0.68 [0.36, 1.27] TEMSO: 0.69 [0.58, 0.81] TOWER: 0.64 [0.53, 0.77] Direct MA: 0.664 [0.589, 0.749]
Betaferon 250µg vs. Placebo	0.68 [0.52, 0.88]	[redacted]	[redacted]	
Avonex 30µg vs. Placebo	0.78 [0.67, 0.91]	[redacted]	[redacted]	
Rebif 44 mg vs. Placebo	0.62 [0.51, 0.76]	[redacted]	[redacted]	
GA 20 mg vs. Placebo	0.64 [0.53, 0.76]	[redacted]	[redacted]	CONFIRM: 0.72 [0.61, 0.87]
Fingolimod 0.5 mg vs. Placebo	0.46 [0.40, 0.54]	[redacted]	[redacted]	Kaposi L, 2010: 0.45 [0.37, 0.54] Saida, 2012: 0.51 [0.27, 0.95] Calabresi, 2012: 0.52 [0.43, 0.64] Direct MA: 0.486 [0.425, 0.556]
Natalizumab 300 mg vs. Placebo	0.31 [0.25, 0.39	[redacted]	[redacted]	Polman, 2006: 0.32 [0.27, 0.37]
Teriflunomide 14mg vs. Betaferon 250µg	0.98 [0.73, 1.31]	0.97 [0.80, 1.18]	0.94 [0.72, 1.25]	
Teriflunomide 14mg vs. Avonex 30µg	0.86 [0.69, 1.05]	0.84 [0.71, 1.00]	0.78 [0.61, 1.01]	
Teriflunomide 14mg vs. Rebif 44 µg	1.06 [0.84, 1.35]	1.04 [0.84, 1.28]	0.99 [0.77, 1.30]	[redacted]
Teriflunomide 14mg vs. GA 20 mg	1.05 [0.83, 1.31]	1.01 [0.85, 1.21]	0.99 [0.79, 1.24]	
Teriflunomide 14mg vs. Fingolimod 0.5 mg	1.45 [1.17, 1.80]	[redacted]	1.41 [1.14, 1.77]	
Teriflunomide 14mg vs. Natalizumab 300 mg	2.12 [1.63, 2.75]	[redacted]	2.10 [1.61, 2.76]	

Table 2: MTC results 3mth SAD

	Base case analysis	All Years analysis	Adjusted All Years analysis	Direct results available*
Comparison	**Hazard ratio [95% CrI]**	**Hazard Ratio [95% CrI]**	**Hazard Ratio [95% CrI]**	**Hazard Ratio [95% CrI]**
Teriflunomide 14mg vs. Placebo	0.71 [0.53, 0.92]	[redacted]	[redacted]	TEMSO: 0.7 [0.51, 0.96]; TOWER[redacted] Direct MA: 0.694 [0.544, 0.886]
Betaferon 250µg vs. Placebo	1.21 [0.68, 2.16]	[redacted]	[redacted]	IFNB Study, 0.68 (95% CI 0.40, 1.17)
Avonex 30µg vs. Placebo	0.91 [0.61, 1.33]	[redacted]	[redacted]	Data only for 6mth SAD
Rebif 44 µg vs. Placebo	0.79 [0.51, 1.24]	[redacted]	[redacted]	PRISMS, 0.65 (95% CI 0.45, 0.94)
Rebif 22 µg vs. Placebo		[redacted]	[redacted]	
GA 20 mg vs. Placebo	0.93 [0.59, 1.45]	[redacted]	[redacted]	CONFIRM: 0.93 [0.63, 1.37]
Fingolimod 0.5 mg vs. Placebo	0.75 [0.58, 0.96]	[redacted]	[redacted]	
Natalizumab 300 mg vs. Placebo	0.58 [0.4, 0.84]	[redacted]	[redacted]	Polman, 2006: 0.58 [0.43, 0.78]
Teriflunomide 14mg vs. Betaferon 250µg	0.58 [0.30, 1.12]	0.75 [0.49, 1.24]	0.59 [0.34, 1.03]	
Teriflunomide 14mg vs. Avonex 30µg	0.77 [0.50, 1.24]	0.80 [0.51, 1.23]	0.72 [0.46,1.16]	
Teriflunomide 14mg vs. Rebif 44µg	0.90 [0.54, 1.45]	0.97 [0.66, 1.43]	0.82 [0.54,1.27]	[redacted]
Teriflunomide 14mg vs. Rebif 22µg		[redacted]	[redacted]	
Teriflunomide 14mg vs. GA 20 mg	0.76 [0.45, 1.30]	0.90 [0.60, 1.37]	0.76 [0.49, 1.20]	
Teriflunomide 14mg vs. Fingolimod 0.5 mg	0.95 [0.64, 1.35]	[redacted]	0.91 [0.63, 1.29]	
Teriflunomide 14mg vs. Natalizumab 300 mg	1.22 [0.77, 1.94]	[redacted]	1.14 [0.73,1.8]	

Table 3: Table MTC results Discontinuations

	Base case analysis	All Years analysis	Adjusted All Years analysis	Direct results available*
Comparison	**Odds ratio [95% CrI]**	**Odds ratio [95% CrI]**	**Odds ratio [95% CrI]**	**Odds ratio [95% CrI]**
Teriflunomide 14mg vs. Placebo	[redacted]	[redacted]	[redacted]	O'Connor P, 2006: 3.8 [1.15, 12.58] TEMSO: 0.9 [0.65, 1.25] TOWER: 1.07 [0.79, 1.45] Direct MA: [redacted]
Betaferon 250µg vs. Placebo	[redacted]	[redacted]	[redacted]	
Avonex 30µg vs. Placebo	[redacted]	[redacted]	[redacted]	
Rebif 22 µg vs. Placebo	[redacted]	[redacted]	[redacted]	
Rebif 44 µg vs. Placebo	[redacted]	[redacted]	[redacted]	
GA 20 mg vs. Placebo	[redacted]	[redacted]	[redacted]	CONFIRM: 0.59 [0.43, 0.81]
Fingolimod 0.5 mg vs. Placebo	[redacted]	[redacted]	[redacted]	Kaposi L, 2010: 0.61 [0.44, 0.85] Saida, 2012: 1.59 [0.53, 4.82] Direct MA: 0.848 [0.348, 2.068]
Natalizumab 300 mg vs. Placebo	[redacted]	[redacted]	[redacted]	Polman, 2006: 0.81 [0.54, 1.2]
Teriflunomide 14mg vs. Betaferon 250µg	2.10 [1.22, 3.50]	1.56 [0.95, 2.49]	1.93 [1.19, 3.04]	
Teriflunomide 14mg vs. Avonex 30µg	1.13 [0.71, 1.82]	1.04 [0.66, 1.60]	1.18 [0.74, 1.84]	
Teriflunomide 14mg vs. Rebif 22µg		[redacted]	[redacted]	
Teriflunomide 14mg vs. Rebif 44µg	0.80 [0.54, 1.30]	0.74 [0.51, 1.10]	0.88 [0.60,1.26]	[redacted]
Teriflunomide 14mg vs. GA 20 mg	1.50 [1.02, 2.23]	1.28 [0, 89, 1.84]	1.47 [1.02, 2.05]	
Teriflunomide 14mg vs. Fingolimod 0.5 mg	1.46 [0.96, 2.12]	[redacted]	1.52 [1.01, 2.17]	
Teriflunomide 14mg vs. Natalizumab 300 mg	1.27 [0.76, 2.10]	[redacted]	1.34 [0.82, 2.22]	

Section 3: Review of the manufacturer's updated model

The manufacturer's updated model included the ERG's preferred scenarios including,

- Natural history progression data from placebo arms of TOWER and TEMSO
- Initial EDSS distribution from TOWER and TEMSO
- ERG amended calculation from SPMS conversion probabilities
- Direct non-medical costs not included
- Utilities observed in TEMSO, using increments from Orme for high EDSS states where trial data were not available

There were small differences between the ERG's reported ICERs and those calculated from the manufacturer's model removing the committee's requested changes to the MTC and waning effects.

Comparing teriflunomide to glatiramer acetate, the ERG reported an ICER of £86,946 per QALY compared to the manufacturer's model result of £85,751 per QALY. The ERG further explored the manufacturer's model and found 3 reasons for the differences.

1. A small rounding difference in the SPMS transitions from the manufacturer using the ERG's reported numbers rather than recalculating these numbers.
2. A calculation error in the ERG's model, sheet 'Defaults' cell AE41, resulting in a 0.01 difference in the probability of hospitalisation due to relapse.
3. The manufacturer also changed the baseline characteristics to match the TOWER and TEMSO data rather than using the baseline characteristics from the UK RSS as was done by the ERG. This difference resulted in the biggest change in the ICER. The manufacturer's model result increased to 86,390 when the UK RSS baseline characteristics were used.

All further analyses were done using the manufacturer's updated model, as the model differences result in very small differences in the ICER and in the case of the probability of hospitalisation the manufacturer's model is correct.

The manufacturer has focused their analyses on the comparison of teriflunomide versus glatiramer acetate because it is the only treatment that is cost-effective compared to teriflunomide in the ERG's preferred analysis. The manufacturer demonstrates that the comparison with glatiramer acetate relies on 3 clinical trials and is strongly influenced by a small trial (n=50) that suggests glatiramer acetate is highly effective (HR=0.32, 95%CI: 0.09 to 1.09) compared to placebo contrary to the other 2 trials in larger populations that suggest that its effectiveness is only modest (HR=0.93/ HR=0.86) although neither are statistically significant. The manufacturer argues that this trial should be considered an outlier based on its numerical difference but no clinical justifications are given for its exclusion. Even so, the manufacturer included this trial in their adjusted MTC; the ERG agrees with

this decision which is conservative towards teriflunamide. All further analyses include all three trials of glatiramer acetate.

The manufacturer presents the fully incremental probabilistic analysis following the committee's request. The manufacturer uses the ERG's preferred analysis, i.e. natural history progression data from placebo arms of TOWER and TEMSO, initial EDSS distribution from TOWER and TEMSO, the ERG amended calculation from SPMS conversion probabilities, excluding the direct non-medical costs and using the utilities observed in TEMSO and increments from Orme for high EDSS states where trial data were not available. The manufacturer also used the results of the adjusted MTC and included waning of treatment effect to 75% at 2 years and 50% beyond 5 years. Finally the manufacturer also used the base case characteristics of the TEMSO and TOWER trial. These results suggest that teriflunomide is cost-effective compared to glatiramer acetate with an ICER of £13,234 per QALY and that teriflunomide is more effective and less costly than the other treatments. The ERG found similar results when re-estimating the manufacturer's model although small differences were found due to a different run of the Monte Carlo simulation.

Table 4: ERG's re-estimation of the manufacturer's Table 1: Probabilistic results of teriflunomide versus all comparators (using all years MTC adjusted for baseline ARR)

	Cost (£)	QALYs	ICER (£ per QALY)
glatiramer acetate	[redacted]	[redacted]	-
teriflunomide	[redacted]	[redacted]	£ 13,972
IFNβ -1a 44mcg (Rebif)	[redacted]	[redacted]	Dominated
IFNβ -1a (Avonex)	[redacted]	[redacted]	Dominated
IFNβ -1a 22mcg (Rebif)	[redacted]	[redacted]	Dominated
IFNβ -1b	[redacted]	[redacted]	Dominated

The manufacturer also presents a comparison of teriflunomide versus glatiramer acetate using the three methods for estimating the MTC and with and without waning (Manufacturer's Tables 2 and 3). These tables show that the ICER's from the adjusted MTC are much more similar to the post-2000 MTC that only uses trials after the year 2000 (ICER= £9,216) than to the all years MTC (ICER=£118,554). A comparison of the manufacturer's Tables 2 and 3 demonstrate that the probabilistic ICERs are very similar although slightly lower than the deterministic ICERs. The deterministic results presented by the manufacturer in Table 3 of the manufacturer's submission for the data request were all verified by the ERG.

As discussed in section 2 the main differences in the model inputs between the 'All years MTC' and the MTC adjusted for baseline ARR are the disease progression and withdrawal rates. The model inputs for disease progression using the 'All years MTC' are [redacted] for teriflunomide and glatiramer acetate respectively. Using the MTC adjusted for baseline ARR the model inputs for disease progression are [redacted]. Using the manufacturer's new analysis (with the ERG preferences, waning and adjusted MTC) except for the disease progression inputs from the 'All years MTC' (i.e. RR[redacted] for teriflunomide and [redacted] for glatiramer acetate) results in an ICER of £109,237 per QALY. This demonstrates the sensitivity of the model to the disease progression inputs and that

the majority of the difference in the new ICERs presented by the manufacturer is due to the difference in the estimated disease progression.

The other main difference in the MTCs is the difference in withdrawal rates. Although the differences within treatments are relatively small for teriflunomide the rates do not change between the 'All years MTC' and the 'adjusted MTC'; for glatiramer acetate the rates are 0.128 and 0.114 for the 'All years MTC' and the 'adjusted MTC' respectively. However, a 0.014 difference in the withdrawal rate has a large effect on the ICER. Using the manufacturer's new analysis (with the ERG preferences, waning and adjusted MTC) except for withdrawal rate inputs from the 'All years MTC' (i.e. 0.128 for glatiramer acetate) results in an ICER of £22,797 per QALY. This demonstrates the sensitivity of the model to the withdrawal rate inputs and that small changes in the withdrawal rates may change the decision. If glatiramer acetate is assumed to have the same withdrawal rate as teriflunomide the ICER increases to £32,971 per QALY. As described previously by the ERG this also demonstrates the perversity of the model, that a treatment is more cost-effective the higher the withdrawal rate.

Section 4: Review of the manufacturer's sensitivity analysis including direct non-medical costs

The manufacturer also presents a sensitivity analysis including 'Other direct costs' otherwise called the direct non-medical costs. The probabilistic analysis presented in the manufacturer's Table 5, suggests that when direct non-medical costs are included teriflunomide is less costly and more effective than all other treatments. The deterministic analysis undertaken by the ERG resulted in teriflunomide being less costly and more effective than all comparators except glatiramer acetate for which teriflunomide was more costly and more effective with an ICER of £2,679 per QALY. The probabilistic analysis undertaken by the ERG (Table 5) resulted in slightly different estimates of the costs and QALYs with direct non-medical costs from Tyas et al. included in the analysis.

Table 5: ERG's re-estimation of the manufacturer's Table 5: Sensitivity analysis: probabilistic results of teriflunomide versus all comparators including direct non-medical costs.

	Cost (£)	QALYs	ICER (£ per QALY)
glatiramer acetate	[redacted]	[redacted]	-
teriflunomide	[redacted]	[redacted]	£ 124
IFNβ -1a 44mcg (Rebif)	[redacted]	[redacted]	Dominated
IFNβ -1a 22mcg (Rebif)	[redacted]	[redacted]	Dominated
IFNβ -1a (Avonex)	[redacted]	[redacted]	Dominated
IFNβ -1b	[redacted]	[redacted]	Dominated

These sensitivity analyses including the Tyas et al. costs are based on a justification from the manufacturer that although there are no details available in the Tyas paper to help us understand what is included in direct non-medical costs, the reported costs by EDSS score are similar to those reported by Karampampa et al. for which there is some detail about what is being reported. The manufacturer uses their Table 4 to support this statement. In reviewing the manufacturer's Table 4

the ERG do not find the direct non-medical costs between Tyas et al. and Karampampa et al. to be similar. This is particularly true in the EDSS scores less than 7: in EDSS scores less than 4 the costs from Karampampa are more than 100 times less than the costs reported in Tyas et al, i.e. £5,335 and £53 in EDSS 0 to £9,565 and £53 in EDSS 3, from Tyas et al. and Karampampa et al., respectively.

The ERG further considered the details of the Karampampa et al. direct non-medical costs. These costs included patients' estimations of investments in the last 12 months on wheel chair, scooter, or transformations to their house or car. These costs also included patients' estimations of the hours of professional care in the last 3 months including nurses, home help and other professional help. Annual resource use was calculated by assuming 3 month use would be the same across the year and multiplying the 3 month use by 4. Annual resource use was multiplied by unit costs to estimate annual costs. Details of the unit costs used were not well reported.

The ERG add a further sensitivity analyses around costs using the midpoint of the Karampampa et al – 66% reported by the manufacturer (Table 6). In the deterministic analysis teriflunomide is more effective and less costly than all of the beta interferons but is more costly than glatiramer acetate with an ICER of £2,729 per QALY. In the probabilistic analysis all comparators are less effective and more costly than teriflunomide. Although the deterministic ICER comparing teriflunomide to glatiramer acetate is higher using Tyas et al. than 66% Karampampa et al. the probabilistic ICER is lower, this difference is due to the variability inherent in probabilistic analyses. However, the conclusions across all of these analyses are the same, that teriflunomide is the cost-effective option when direct non-medical costs are included.

Table 6: Sensitivity analysis: probabilistic results of teriflunomide versus all comparators including 66% of the direct non-medical costs from Karampampa et al.

	Cost (£)	QALYs	ICER (£ per QALY)
teriflunomide	[redacted]	[redacted]	-
glatiramer acetate	[redacted]	[redacted]	Dominated
IFNβ -1a 44mcg (Rebif)	[redacted]	[redacted]	Dominated
IFNβ -1a (Avonex)	[redacted]	[redacted]	Dominated
IFNβ -1a 22mcg (Rebif)	[redacted]	[redacted]	Dominated
IFNβ -1b	[redacted]	[redacted]	Dominated

Section 5: Review of the manufacturer's exploration of treatment sequencing

As requested by the committee the manufacturer presented the cost-effectiveness of selected sequences. The probabilistic results presented by the manufacturer could not be matched but were similar to the deterministic results, i.e. the same in scenario 1 and £38,200 versus £40,458 per QALY in scenario 2 (Table 7). The fingolimod treatment effect used by the manufacturer in scenario 1 is for RRMS patients; however fingolimod is not approved in this population. The manufacturer presents a number of other selected scenarios, none of which include glatiramer acetate, the only treatment not dominated by teriflunomide in previous analyses, as the first line treatment. Further, additional analyses presented by the manufacturer including natalizumab also used treatment effects for the RRMS population for which natalizumab is not recommended. Finally, treatment

effects for each treatment were assumed to be the same when used as first, second, or third-line. Alternatively the manufacturer could have assumed declining treatment effectiveness with further lines of therapy. The ERG expects that this alternative assumption would increase the ICER of teriflunomide because of its higher withdrawal rate.

Table 7: Treatment sequencing scenarios requested by the committee using the adjusted MTC

Scenario	First-line	Second-line	Third-line	Comparator First-line	Comparator Second-line	Comparator Third-line	ICER £ per QALY (Deterministic)
1	Teriflunomide	Rebif-44	Fingolimod	Rebif-44	Fingolimod	BSC	Teriflunomide line dominates comparator line
2	Teriflunomide	Rebif-44	Glatiramer acetate	Rebif-44	Glatiramer acetate	BSC	38,200 (40,458)

Table 8: Some additional treatment sequencing scenarios presented by the manufacturer using the adjusted MTC

Scenario	First-line	Second-line	Third-line	Comparator First-line	Comparator Second-line	Comparator Third-line	ICER £ per QALY (Deterministic)
3	Teriflunomide	Rebif-44	Glatiramer acetate	Rebif-44	Glatiramer acetate	BSC	38,200
4	Teriflunomide	Glatiramer acetate	BSC	Rebif-44	Glatiramer acetate	BSC	Teriflunomide line dominates comparator line

The sequencing analysis highlights the difference in cost-effectiveness when it is assumed that teriflunomide is added to current therapy rather than replacing an existing therapy. This is demonstrated by the manufacturer's scenarios 3 and 4 in the manufacturer's Table 10, these scenarios are reproduced for convenience (Table 8). This comparison demonstrates that adding an additional treatment to the sequence as in scenario 3 results in teriflunomide having an ICER greater than £30,000, whereas if teriflunomide replaces a treatment as in scenario 4 the teriflunomide line is more effective and less costly.

To understand the reason why adding teriflunomide as an additional therapy increased the ICER of the treatment sequence the ERG explored the cost-effectiveness of teriflunomide compared to BSC (Table 9). Using the adjusted MTC and the ERG's preferred base case, only in the scenarios where there are no waning effects and direct non-medical costs are included is teriflunomide cost-effective compared to BSC at a £30,000 per QALY threshold. This explains the reason adding teriflunomide as an additional therapy is not cost-effective in the manufacturer's scenarios above since adding an additional therapy prolongs the time until patients are treated with the most cost-effective option, BSC.

Table 9: Deterministic ICERs of teriflunomide versus BSC using the MTC adjusted for baseline ARR

Comparators	Waning	Direct non-medical costs	ICER (£ per QALY)
Terfiflunomide versus BSC	75% at 2 years, 50% at 5 years	none	£64,032
Terfiflunomide versus BSC	none	none	£42,243
Terfiflunomide versus BSC	75% at 2 years, 50% at 5 years	Tyas et al.	£50,743
Terfiflunomide versus BSC	none	Tyas et al.	£29,293
Terfiflunomide versus BSC	75% at 2 years, 50% at 5 years	66% Karampampa et al.	£50,602
Terfiflunomide versus BSC	none	66% Karampampa et al.	£29,289

The manufacturer provides conflicting opinions from their Key Opinion Leaders in the manufacturer's original submission stating "Having reviewed publicly available trial evidence for teriflunomide, the clinicians stated they would, subject to guidance, expect to use teriflunomide at first line as an alternative to beta-interferons or glatiramer acetate. Therefore, the availability of teriflunomide is not expected to increase the number of lines of therapy received by a patient." However, the manufacturer also states that "in UK clinical practice, a patient is more likely to receive an alternative DMT than BSC, following withdrawal from their first or second-line DMT ". If clinicians are more likely to continue DMTs then teriflunomide may be considered an additional rather than a replacement treatment.

The manufacturer states that the consideration of teriflunomide has been incorrectly restricted to first-line treatment. However, no sub-group analyses in further lines of treatment were explored clinically in the manufacturer's submission. All cost-effectiveness analyses are contingent on teriflunomide and its comparators performing the same in previous lines of treatment as in first-line treatment, however no evidence for this assumption has been provided. The ERG has restricted its

evaluation and discussion of teriflunomide to first-line treatment due to the lack of robust evidence in further lines of treatment.

Section 6: Review of the manufacturer's external model validation

As requested by the committee the manufacturer presents a comparison of the results from TA 32 to the results of the manufacturer's model. The ICERs presented by the manufacturer (£139,930 per QALY for glatiramer acetate to dominated for Betainterferon) are less cost-effective versus placebo than those presented previously in TA 32 (£48,085 for Avonex to £97,690 for glatiramer acetate). The manufacturer also presents 2 year model results compared to the 2 year results from the UK risk-sharing scheme (Boggild et al. 2009). The actual progression on DMTs reported in the UK RSS is higher than the progression estimated in the manufacturer's model however, contrary to expectations the health related quality of life estimated in the manufacturer's model is lower. Therefore the manufacturer's model predicts slower progression but lower health related quality of life than the observational data.

The results of the manufacturer's validation suggest that the manufacturer's model does not correspond well with previous analyses of beta interferons and glatiramer acetate (TA 32) or with observational data from the UK RSS (Boggild et al. 2009).