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26th August 2011

Dear Professor Longson

Re: Fingolimod (Gilenya®▼) for the treatment of relapsing remitting multiple sclerosis (RRMS) – Appraisal Consultation Document (ACD).

Thank you for your letter dated 29th July 2011 inviting comments on the above.

Naturally Novartis are disappointed that NICE has not recommended Gilenya at this stage. However, we are encouraged that NICE has recognised the efficacy of Gilenya in people with MS, and that the oral formulation is of benefit compared to the currently available options.

Multiple Sclerosis (MS) is a disabling neurological condition that can affect people in the prime of their life. Disability accrues progressively over years if left untreated. There is considerable variation in the pace, and severity of the disease which is why physicians cycle through a range of treatments throughout an individual's treatment plan. There are several therapies in the first-line of treatment for clinician's to prescribe, all of which have broadly the same efficacy. Unfortunately, there are people with MS who are currently either not responding to these first-line injectable therapies or are responding but continue to have some degree of disease activity which merits consideration of alternate treatment.

Novartis believes Gilenya can specifically address this unmet need for UK patients. We also believe that once the Appraisal Committee has had a chance to consider our response to the draft ACD, we can bring this clinically effective and innovative medicine to those who can achieve the most benefit.

There are elements of the ACD that we view are not wholly consistent with the data provided and in summary these are:

A. Avonex is an appropriate comparator for Gilenya having comparable efficacy to all other interferon preparations. It is associated with good adherence and requires the fewest injections, which is important for quality of life. It is also widely used in the UK.
B. Best supportive care (BSC) does not reflect UK clinical practice in the setting of continued disease activity despite interferon therapy. Of note, a previous NICE technology appraisal of an MS therapy deemed BSC to be an inappropriate comparator (TA 127).
C. Gilenya is a well studied, highly effective, and highly innovative medicine that addresses a current unmet medical need in people with RRMS who are not responding to current first-line interferon therapies.
D. The submission dossier from Novartis was robust and prepared in accordance with the NICE STA methodology.

These points are discussed in greater detail within our response.

We sincerely encourage NICE to reconsider its preliminary guidance in light of our comments. We believe that these points will address the overall comment from NICE relating to uncertainties regarding the clinical effectiveness of Gilenya.

If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely

Avonex is a suitable comparator for Gilenya

In the summary of the ACD (**Section 4.17 Page 30**) it states "Avonex is not an appropriate comparator for population 1b."

Novartis does not agree with this statement. We believe that Avonex* (interferon beta-1a IM) provides a good representation of the beta interferons as a class. We also believe that all the beta interferons are broadly equivalent and there is no evidence which demonstrates that Avonex is consistently significantly inferior to any of the other beta interferons.

The recommendation for Gilenya should be based on a comparison of Gilenya versus Avonex and the ACD should be amended to reflect this. Below is a discussion of the broad evidence base upon which this is based using the following headings:

- Avonex trial data demonstrates that its efficacy is similar and non-inferior to the other beta interferons
- Systematic reviews support the view that all first-line Disease Modifying Therapies (DMTs) are broadly equal in efficacy
- Avonex is more beneficial than placebo in sub-optimally responding patients
- Avonex has unique benefits compared to other beta interferons
- Avonex is widely used in the UK
- There is no clinical data on which to base an alternative economic comparison

1. Avonex trial data demonstrates that its efficacy is similar and non-inferior to that of the other beta interferons

Section 3.26 states "The ERG noted that other beta interferons may have greater efficacy than Avonex" and this belief is used to justify not accepting Avonex as a good representative of the class of interferons.

Avonex has been evaluated in both placebo controlled and active comparator studies.

The pivotal RRMS Avonex study demonstrated a significant benefit compared to placebo for relapse, disability and MRI outcomes.[1] The most recent Phase III randomised clinical study including Avonex is BRAVO. In the Avonex treatment arm there was a 26%-29% reduction of relapse rate versus placebo which was statistically significant.[2] This was a two year study and included patients who had previously received first-line therapies. The magnitude of effect in this study is comparable to that of the pivotal study and comparable to the relapse rate reductions seen with other interferon products.

Novartis have identified nine head-to-head studies which have demonstrated no statistically significant difference between Avonex and other beta interferons; see Table 1 for a summary. As can be seen during the last 10 years a wealth of data has been collected from 9,227 subjects. This data includes head-to-head evaluations from all of the different beta interferons versus Avonex.

* The generic names of the beta interferons are very similar. To aid understanding we have used the trade names for the beta interferons throughout the document: Avonex (Interferon beta 1a), Rebif (Interferon beta-1a), Betaferon (Interferon beta-1b), and Copaxone (Glatiramer acetate).

Table 1: Head-to-head studies of Avonex versus interferon beta products which demonstrate no significant difference between the therapies

Study	Treatment Group	No. Patients	Study Design	Treatment Duration	Efficacy Endpoints	Outcome
Minagar and Murray (2008) PROOF[26]	Avonex Rebif 44	69 67	Prospective / retrospective open label	18-30 months (6 months prospective ; 12-18 months retrospective)	EDSS, relapse rate, % relapse-free patients, MRI disease activity	***No significant differences between IFNs***
Limmroth et al. (2007) QUASIMS.[21]	Avonex Betaferon Rebif 22 Rebif 44	1728 1706 932 388	Retrospective, observational open label	≥ 2 years	Relapse rate, EDSS	***No significant differences between IFNs***
Rio et al. (2006)[3]	Avonex Betaferon Rebif	148 185 136	Observational, open label	2-8 years	Relapse rate, EDSS	***No significant differences between IFNs***
Haas and Firzlaff (2005)[4]	Avonex Betaferon Rebif Copaxone	177 325 114 140	Retrospective, open label	2 years	Relapse rate, % relapse-free patients, % progression-free patients	***No significant differences between IFNs***
Milanese et al. (2003)[5]	Avonex Betaferon	647 834	Prospective, observational, open label	>1 year	% relapse free patients, EDSS	***No significant differences between IFNs***
Trojano et al. (2003)[6]	Avonex Betaferon Rebif 22	217 234 89	Observational, open label, non-randomised	2 years	Relapse rate, EDSS	***No significant differences between IFNs***
Romero-Lopez et al. (2003)[7]	Avonex Betaferon Rebif	81 115 47	Retrospective, open label	2.1 years (mean)	Relapse rate, EDSS	***No significant differences between IFNs***
Panitch et al. (2002) EVIDENCE[24]	Avonex Rebif 44	338 339	Prospective, open label, randomised, assessor blinded	48 weeks	% relapse-free patients, ARR	***No significant differences in annualised relapse rate (ARR) between IFNs at the end of the study***
Ozetekin and Ozetekin (2001)[8]	Avonex Rebif 22 Betaferon	63 36 72	Prospective, open label	2 years	Relapse rate, EDSS	***No significant differences between IFNs***

Avonex (Interferon beta 1a). Rebif (Interferon beta-1a). Betaferon (Interferon beta-1b). Copaxone (Glatiramer acetate).

In terms of head-to-head studies demonstrating a difference; the INCOMIN study compared Betaferon to Avonex in an open label study of 188 subjects.[25] In the primary endpoint, proportion of patients free from relapse, there was a significant (p=0.03) difference between the two groups in favour of Betaferon. However, there are a number of confounding factors that question the validity of the superiority claim of the authors. The study was open-label, leading to potential bias in reporting and recording and underwent unspecified interim analyses. The baseline characteristics between the two arms were significantly different since the ARR for Avonex was 1.38 compared to 1.52 for Betaferon. In addition, there was no significant difference in treated relapses during the study which may have further confused interpretation of these results.

Overall when all of the available clinical trial data is considered it clearly demonstrates that the efficacy of Avonex is comparable to the other beta interferons.

2. Systematic reviews support the view that all beta interferons are broadly equal in efficacy

Systematic reviews have been conducted comparing the beta interferons and have concluded that they have broadly the same efficacy in the treatment of multiple sclerosis.[9,10,11,12] In addition, as part of the NICE MTA of beta interferons and glatiramer acetate the assessment group concluded that the clinical trials do not suggest major differences in the efficacy of different preparations of beta interferon.[13]

Furthermore, in the Novartis submission for Gilenya a Mixed Treatment Comparison (MTC) is presented for the RRMS population. This MTC which followed the NICE methodology also confirmed that all of the beta interferons have broadly the same efficacy when all efficacy endpoints are considered. Maximal efficacy for each endpoint was achieved by different products, highlighting the comparability overall of interferon preparations. For instance, in the Novartis submission in Table 34 (Page 149) we detail the results of the MTC comparing the efficacy of the different DMTs in RRMS in terms of the endpoint 3-month disease progression. The results are reproduced in Table 2 and support the concept that Avonex falls within the range of interferon efficacy on this endpoint.

Table 2: Confirmed disability progression (at 3-months) mixed-treatment comparison results versus placebo

	Relative risk (95% confidence interval)
Betaferon (Interferon-beta-1b 250 mcg)	[redacted]
Rebif-22 (Interferon-beta-1a 22 mcg)	[redacted]
Avonex (Interferon-beta-1a 30 mcg)	[redacted]
Copaxone (Glatiramer acetate 20 mg)	[redacted]
Rebif-44 (Interferon-beta-1a 44 mcg)	[redacted]
Gilenya (Fingolimod 0.5 mg)	[redacted]

Highlighting indicates Academic-in-confidence

This discussion above shows that the statement in **Section 3.26** which states “The ERG noted that other beta interferons may have greater efficacy than Avonex” does not represent the wealth of evidence which shows that the beta interferons are all broadly equivalent. In addition, the discussion here supports the view from Novartis that Avonex is a good representative of the class of interferons.

3. Avonex is more beneficial than placebo in sub-optimally responding patients

Section 3.18 (Page 14) states “Furthermore, the ERG noted that the indirect comparison used in the economic model suggested that Avonex is less beneficial than placebo, which it considered to be further evidence that Avonex is not a suitable comparator for population 1b”. In addition, in **Section 4.11 (Page 27)** it states: “partly because the estimate of effectiveness for Avonex was lower than that for placebo in the indirect comparison that underpinned the analysis.”

Novartis have looked closely at the indirect comparison of Avonex versus placebo and our analysis of Population 1b does not indicate that Avonex is less beneficial than placebo. The only population where Avonex had an apparent lower efficacy was in the modelled data for the population requested by the ERG, “Population 1b but not 2”, and it was only in terms of disease progression. We believe this was a chance event due to the small population size and is not consistent with the results for Population 1b. For the endpoint, relapse reduction, Avonex was superior to placebo in “Population 1b but not 2”.

This misunderstanding by the ERG was noted by Novartis during the five day ERG fact check and was highlighted during the Appraisal Committee Meeting. However, this misunderstanding has been reflected in the ACD. Given that the finding is likely to be an artefact and is technically incorrect, Novartis requests that this information be deleted from the ACD and that NICE are apprised of this information in order to correct any misperceptions that could adversely and unfairly affect the appraisal.

4. Avonex has unique benefits compared to other beta interferons

The main measures of clinical efficacy in MS studies have traditionally been reduction in relapse rate and disability progression. However, there are a number of other measures of clinical benefit which need to be considered when selecting which interferon to choose. This means it is not as simple as comparing one endpoint, such as relapse reduction and using this to rank which interferon is the most “efficacious”.

Of all of the beta interferon preparations, Avonex is the least immunogenic and the least likely to result in the production of neutralising antibodies.[14,15,16] There is significant evidence to suggest that over the long term (at least 18 months), patients who persistently test positive for neutralising antibodies to their beta interferon medication are more likely to display loss of clinical efficacy (relapse and MRI outcomes) versus those patients who remain antibody negative.[17,18,19,20] This view was also the consensus opinion reached by the Neutralizing Antibodies on Interferon Beta in Multiple Sclerosis Consortium in 2009.[16]

Avonex will therefore be more likely to maintain consistent efficacy over the long term than other interferon preparations where clinical efficacy will be reduced if the patient develops neutralising antibodies. This is evident in studies that track real-life use of interferon formulations.[21]

There have been several publications, including the EVIDENCE trial (Avonex vs. Rebif)[24], to suggest that weekly intramuscular (IM) injections of Avonex is less likely to result in abnormal liver enzyme elevations than the other more frequently administered beta interferon preparations, Rebif and Betaferon. Chan (2011)[22] recently reported that Rebif

and Betaferon were associated with a three-fold increase in odds of liver enzyme abnormality compared with Avonex. These findings were consistent with an analysis of hepatic safety data from a Rebif clinical trials database[23] which showed that liver enzyme elevations were more common in high frequency beta interferon preparations than low frequency preparations such as Avonex.

In addition, comparative data from EVIDENCE, INCOMIN and PROOF demonstrated that injection site reactions (a common cause of poor adherence and discontinuation) are less common with Avonex than other beta interferon preparations delivered subcutaneously and with higher frequency.[24,25,26] The SmPC for Avonex lists injection site reactions as occurring at a frequency of 1-10% whereas injection site reactions for the other interferon preparations are listed as very common events occurring at a frequency of ≥10%.

Tolerability issues are known to be linked with poor adherence and drug discontinuation. This is supported by the real-world studies which show that adherence is greater with Avonex than other beta interferons.[27] Greater adherence to therapy will be associated with greater clinical effectiveness.

5. Avonex is widely prescribed in the UK

Section 3.26 (Page 18) states that "Rebif-44 is more commonly prescribed than Avonex in the NHS." In addition, **Section 4.6 (Page 23)** states that "Avonex was not the most commonly prescribed form of beta interferon in the NHS".

Novartis is confident that Avonex is widely used in the UK and the data presented below supports this view. In addition, we believe the beta interferons are prescribed broadly in equal proportions.

All of the beta interferons are generally delivered to the home, so obtaining exact national English and Welsh prescribing data for their use in this population is not possible. Therefore we are unclear how NICE is confident that Rebif-44 is definitely more commonly prescribed than Avonex by the NHS.

Novartis has obtained prescribing data by means of a Freedom of Information (FOI) request from the Prescription Pricing Authority. This data was supplied to the ERG during the clarification questions and it appears in the ERG report. However, it is not discussed in the ACD. Novartis would like to understand why this set of data was omitted from the ACD when it clearly shows that Avonex is widely used in the UK.

Table 3 reproduces this market share data for Disease Modifying Therapies (DMT) use for patients with RRMS from January 2008 to June 2010. It was obtained from 60 primary care trusts. As can be seen Avonex has the highest market share data and is clearly being used by the NHS.

Table 3: Market share of DMTs prescribed for RRMS from Jan 2008 to June 2010

Therapy	Patient share (%)
Interferon-beta-1a (Avonex)	**33.8**
Interferon-beta-1a (Rebif)	28.4
Glatiramer acetate (Copaxone)	21.3
Interferon-beta-1b (Betaferon and Extavia)	16.5

In addition, a market share study conducted in 2010 found that of the RRMS patients receiving a DMT the greatest proportion were receiving Avonex.[28] The results for each DMT are shown in Table 4.

Table 4: Market share of DMTs prescribed for RRMS in 2010

Therapy	Patient share (%)
Interferon-beta-1a (Avonex)	**34**
Interferon-beta-1a (Rebif)	30
Glatiramer acetate (Copaxone)	30
Interferon-beta-1b (Betaferon and Extavia)	7

Finally, in February 2011 the MS Society asked 89 MS centres in England to complete a survey about drug use.[29] Table 5 reports this data and demonstrates that Avonex is used by the vast majority of MS treatment centres in England.

Table 5: Percentage of English MS centres which prescribe different DMTs (February 2011)

Therapy	% of UK centres which prescribe the therapy
Interferon-beta-1a (Avonex)	**92%**
Interferon-beta-1b (Betaferon)	90%
Interferon-beta-1a (Rebif)	90%
Glatiramer acetate (Copaxone)	90%
Interferon-beta-1b (Extavia)	44%

Based on this wealth of evidence Novartis remains confident that Avonex is widely used in the UK and requests that sentences in **Section 3.26** and **Section 4.6** be removed from the ACD to ensure that it is apparent that Avonex is in fact commonly used and thus an appropriate comparator for the NICE appraisal.

6. **There is no clinical data to base an economic comparison for any other beta interferon on**

In **Section 3.26 (Page 18)** there is a discussion of an exploratory analyses conducted by the ERG of Rebif-44 in population 1b. This analysis is described in section 6.3 of the ERG report. In this section of the ERG report the ERG undertook a series of indirect comparisons in "Population 1b" and "Population 1b but not 2" including the therapy Rebif-44. However, the only clinical data available for "Population 1b" or "Population 1b but not 2" is from FREEDOMS and TRANSFORMS. FREEDOMS contained the treatment arms Gilenya and placebo. TRANSFORMS contains the treatment arms Gilenya and Avonex. Following a systematic review, to our knowledge, no comparable controlled data exists for Rebif-44 or any other beta interferon apart from Avonex in sub-optimally responding patients despite prior interferon therapy.

It would appear that the ERG have assumed the efficacy of Rebif-44 and then conducted a series of cost effectiveness analyses based on this which is summarised in **Section 3.26 (Page 18)** of the ACD.

Novartis would challenge whether this approach is appropriate in the absence of actual data. Novartis would encourage NICE to investigate the foundation of the ERG's analysis before reaching a conclusion. As this section is not evidence based, Novartis requests removal of **Section 3.26 (Page 18)** from the ACD.

Section 4.3 (Page 22) reports that the committee heard that "...treatment with natalizumab may be considered for people without rapidly evolving severe disease who experience frequent relapses while on treatment."

Novartis would like to highlight that natalizumab is specifically not recommended by NICE for this population (TA 127). In the manufacturer's submission for natalizumab no specific clinical data was presented for natalizumab for use in the sub optimal therapy (SOT) population and NICE concluded that there was no direct evidence about the clinical effectiveness of natalizumab in these patients.

Novartis suggests that a clarification be added to this sentence in **Section 4.3** that any use of natalizumab in the SOT population is not recommended by NICE.

In summary, Novartis disagrees with the ACD about the choice of comparator to Gilenya. We believe the data presented above supports our view that:

- All the beta interferons are broadly equivalent in efficacy
- Avonex provides a good representation of this class of therapies
- Avonex is widely used in the UK
- The recommendation for Gilenya should be based on a comparison of Gilenya versus Avonex
- The ACD should be amended to reflect this conclusion

A. Best supportive care does not reflect UK clinical practice

Novartis notes that in multiple places in the ACD it argues that best supportive care (BSC) is a more suitable comparator for this appraisal than Avonex.

In addition, we note that most of the incremental cost-effectiveness ratios (ICERs) quoted in the ACD compare Gilenya to BSC. Novartis is confident that beta interferons are used in the UK in patients who have continued disease activity despite use of a beta interferon and below is a discussion of this evidence.

Section 3.18 (Page 13) argues that if a patient experiences disease activity on one beta interferon they would not switch to an alternative preparation of beta interferon. In addition, in **Section 4.3** it states that the Committee believes that clinicians are unlikely to prescribe a different beta interferon after a sub optimal response. **Section 3.18 (Page 13)** argues that best supportive care (BSC) would be a more appropriate comparator. In addition, the conclusion of the ACD (**Section 4.19**) to justify not recommending Gilenya is based on these comparisons versus BSC.

It is worth noting that there is a subtle, but important, distinction between not optimally effective to suppress disease activity and progression, and the therapy being “ineffective”. We believe this distinction does not seem to have been appreciated by the Appraisal Committee.

As presented in Section A of this response, the beta interferons differ with regard to solvents, excipients, interferon type, dose, mode of administration, side effect profile and frequency of administration. Thus it is not unreasonable that if a patient does not respond completely to one preparation, the clinician may opt to treat the patient with a different formulation. There have been clinical studies evaluating the efficacy of DMT switches in sub-optimal responder patients, and in every case a reduction in ARR and disease activity was reported.[30,31,32]

Novartis believes it is clear that BSC (withdrawing beta interferon treatment) in these patients does not reflect UK clinical practice and this has been confirmed by 53 UK expert MS clinicians.

This is further supported by published UK Risk Share Scheme data which documents current UK clinical practice and has recorded the proportion of patients switching between DMTs to increase from 3.9% (1st annual review) to 8.2% (2nd annual review) and 13.6% (3rd annual review).[33]

Given that DMT switching in sub-optimal responding patients is routine clinical practice in the UK, and has been associated with enhanced efficacy, Novartis maintains that active treatment remains the appropriate comparator rather than BSC.

It is also worth noting that this is not the first time NICE has considered the question of appropriate comparator for SOT patients in the UK. Therefore, there is a historic process precedent about which comparator is appropriate for SOT. During the natalizumab STA

(TA127), NICE rejected the use of BSC as a comparator. This was widely supported by both the clinical community and patient groups as not reflective of current clinical practice.

With BSC previously deemed inappropriate as a comparator, Novartis maintain that an interferon is the appropriate comparator for Gilenya. As discussed above in Section A, given that all of the interferon beta products are broadly equal in terms of efficacy, Avonex is a good representative of the class.

Given that BSC does not reflect UK clinical practice Novartis requests that all references to BSC and all cost-per-QALY analyses compared to BSC should be removed from the ACD.

C. Gilenya is a well studied, clinically effective, and highly innovative medicine

Section 3.17 of the ACD questions whether the power calculations give a strong indication of the trials' ability to assess Gilenya relative to the comparators in the populations covered by the marketing authorisation. This discussion is also restated in **Section 4.7 (Page 25)**. We believe this does not reflect the data for Gilenya.

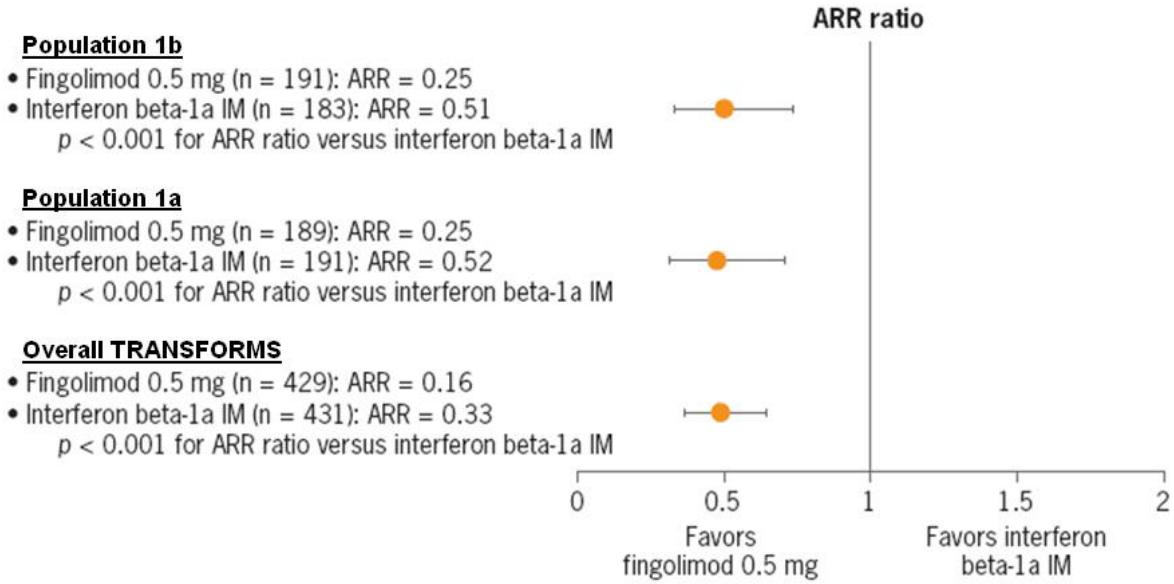
The pivotal studies for Gilenya were powered for the primary and secondary endpoints in the intention to treat (ITT) population. Evaluation of subgroups is permissible assuming success with the primary analyses. Given that the groups are de facto smaller, they cannot retain the same power. The main objective of such sub-analyses is to determine if particular subgroups are deriving substantially different efficacy compared to the overall population, assuming biologic plausibility. Directional and effect size consistency are more relevant than p-values.

In the European public assessment report (EPAR) the Committee for Medicinal Products for Human Use (CHMP) state that the results in the highly active sub-populations were consistent with those obtained in the overall trial population.[34] This demonstrates that even though the subgroup patient pool is smaller the results are credible. The CHMP concluded that the efficacy in reducing the number of relapses was demonstrated in patients with RRMS with high disease activity in the proposed dosing regimen for Gilenya. This is reflected in section 5.1 of the Gilenya Summary of Product Characteristics (SPC) where it states: "Further analyses of clinical trial data demonstrate consistent treatment effects in highly active subgroups of relapsing remitting multiple sclerosis patients."

Novartis believe that if the European Medicines Agency (EMA) had felt that Gilenya did not have clinical efficacy in the licensed population then the EMA would not have granted this particular licence for Gilenya.

Further analyses of clinical trial data demonstrate consistent treatment effects in highly active subgroups of RRMS patients. This data was presented in the Novartis NICE submission and the Annualised Relapse Rate (ARR) data is reproduced in Figure 1. This data clearly shows that Gilenya is efficacious in the subgroups of the licence.

Figure 1: ARR and ARR ratios for Gilenya (fingolimod) versus Avonex (interferon beta-1a IM) during months 0-12 of TRANSFORMS



Error bars represent the upper and lower confidence limits.
Population 1b comprised patients who had received DMT in the year prior to study, but had an unchanged or increased relapse rate in the year prior to study (year –1) compared with the previous year (year –2).Population 1a comprised patients who had received DMT in the year prior to study, but had ≥ 1 relapses in the year prior to study and ≥ 1 Gd-enhancing lesions at baseline or total T2 lesion volume of > 0.5 mL at baseline.

In the NICE appraisal of natalizumab the manufacturer faced a similar problem of having trial data that was from a broader population than the licensed population (NICE TA 127). NICE was able to recommend natalizumab for RES based on a subgroup of 209 subjects from a single placebo controlled study AFFIRM.[35] That subgroup represented only 22% of the subjects in the AFFIRM study.

In the Novartis submission, the data for Population 1b is from 543 subjects from two randomised controlled trials; one placebo controlled and one Avonex controlled. This represents 32% of subjects from both trials. This sample of 543 subjects is over twice the size of that from the single placebo controlled study on which natalizumab received a positive NICE recommendation.

Based on the robust clinical evidence and licensing authorisation granted by the CHMP and EMA, we request that **Section 3.17(Page 13)** and **Section 4.7 (Page 25)** ought to be modified or removed from the ACD to reflect that the data for Gilenya do show good evidence of efficacy in the licensed subgroups.

The appraisal should focus on Population 1b

As discussed in the Novartis submission the Gilenya licence can be considered in three parts with some potential overlap. Figure 2A shows the overlap in the trial population. Novartis chose to focus on Population 1b for the economic analysis, see Figure 2 A. However, during the ERG clarification questions the ERG chose to focus on Population "1b but not 2", see Figure 2 B.

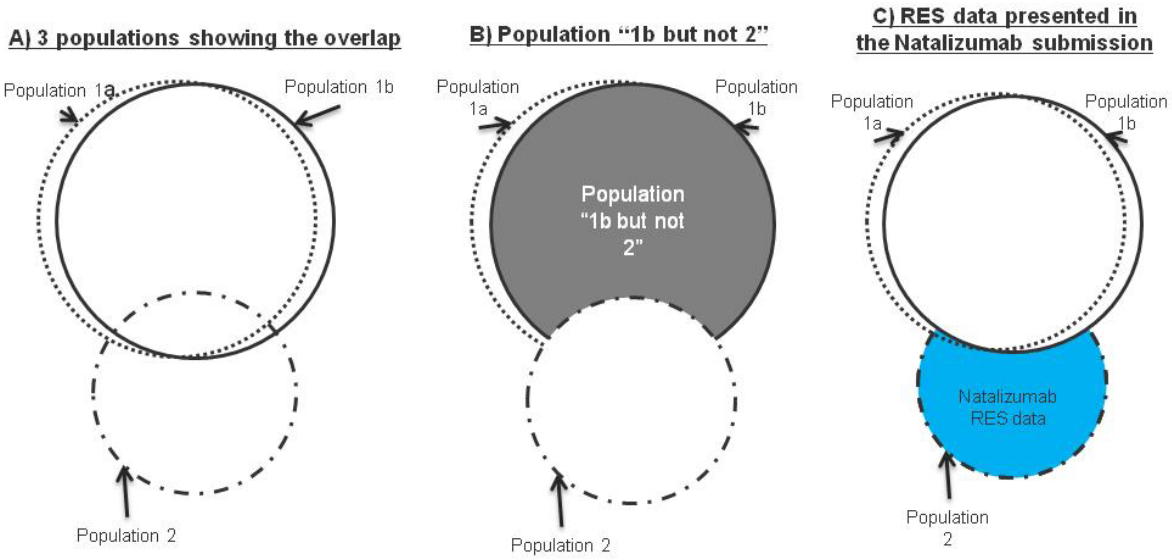
The ERG rationalised that in Population 1b there could be patients who would also meet the criteria for Population 2, and thus the comparator for these patients should be natalizumab. Novartis are unclear if this approach is consistent with the available data.

During the NICE appraisal of natalizumab the data presented by the manufacturer for the RES population (Population 2) of natalizumab is entirely treatment naive,[36] represented by Figure 2 C. As can be seen in Figure 2 C there is no overlap between the natalizumab RES data and Population 1b. In addition, Population 1b by definition is treatment experienced. This suggests that the NICE recommendation for natalizumab is broader than the available natalizumab data. This lack of natalizumab data for Population 1b suggests that the approach of excluding Population 2 (RES) patients from Population 1b in the fingolimod appraisal does not reflect the available data for natalizumab.

Therefore, Novartis disagrees with the ERG about the overlap between Population 1b and 2. Novartis believes that Gilenya should be appraised for the entire Population 1b. In addition, we believe natalizumab should have been appraised for just treatment naive RES patients (i.e. "Population 2 but not 1b).

If Population 1b is considered for Gilenya, this subgroup is a larger group than Population "1b but not 2," and so will have greater certainty.

Figure 2: Venn diagrams of the populations



D. The submission dossier from Novartis was robust and followed the NICE methods guide

Novartis were surprised by the level of criticism in the draft ERG report about the robustness of the Novartis submission. In addition, we were disappointed to have not had the opportunity to properly discuss the concerns from the ERG prior to the production of their report.

We believe some of the criticism is based on a misunderstanding of the Novartis submission and in this section we have provided further details to aid understanding.

Novartis believes the submission was robust because:

- The data was selected in a systematic manner and better dialogue at the ERG clarification stage would have demonstrated this
- The inclusion of adverse events into the economic model was undertaken in a systematic manner
- The effect of using Hazard Ratios as advised by the ERG would make Gilenya more cost-effective, i.e. **reduce the cost-per-QALY**
- The impact of different assumptions of the monitoring costs or relapse cost have a **negligible impact on the cost-per-QALY**
- Using the utility data (EQ5D) from the trials as advised by the ERG would make Gilenya more cost-effective, i.e. **reduce the cost-per-QALY**

Novartis believes the submission was robust and that much of the criticism should be removed from the ACD.

1. ERG criticism of the Novartis approach to identifying and selecting data for the model

Section 3.19 (Page 14) states "The ERG considered that the manufacturer had not used a systematic approach to identify and select appropriate data sources to inform the parameters in the model."

All of the inputs into the model have been identified and selected using a systematic approach. Novartis have examined the ERG report and can find no examples cited by the ERG showing a lack of a systematic approach. Novartis raised this concern during the five day ERG report fact check and we note that the ERG have responded by clarifying the ERG is specifically concerned about the selection of inputs for the natural history progression, relapse conversion, and mortality. Novartis provided information regarding the search used and selection criteria for the inputs. However, the ERG has not presented any alternative literature which contradicts the data selected by Novartis for the natural history progression, relapse conversion, or mortality. In the absence of evidence to support the ERG's perspective we request that NICE remove this sentence in **Section 3.19**.

2. ERG criticism of the method used to derive some of the parameters in the model

Section 3.19 (Page 14) states “In addition, the ERG noted that the methods used by the manufacturer to derive various parameters were not adequately described in the submission and insufficient justification was given for some of the model assumptions.”

The NICE STA template is very comprehensive and manufacturers are advised that the main body of the submission should not usually exceed 100 pages. This means that manufacturers can not go into as much detail as they would prefer for every part of the template. However, there is the ERG clarification question stage which allows the ERG to raise any questions they have about the methodology if the submission is too brief.

In this appraisal the ERG did not take the opportunity to ask Novartis any questions relating to the methodology of deriving the parameters in the model. Instead the ERG appears to have assumed that the methodology undertaken by Novartis is not adequate. Novartis is disappointed that the ERG did not take the opportunity to ask for further clarification as the company believes that the ERG would have been satisfied with the methodology upon further explanation.

Novartis would welcome the opportunity to provide more detailed information on the methodology to remove any questions NICE may have as a result of the ERG conclusion.

It is hoped that upon review of such material, the ERG would agree that the methodology was sound and NICE would remove the statement from the ACD.

3. The cost of relapse used in the model has limited impact on the cost-per-QALY

The ACD states in **Section 3.21 (Page 15):** “In addition, the ERG noted that the cost of relapse used in the model was significantly different from the cost of relapse in other data sources and in NICE technology appraisal guidance 127.”

During the systematic review Novartis had identified the 2010-11 NHS National Tariff for non-elective multiple sclerosis related procedures (AA30Z) as the most credible input for the economic model for the cost of relapses.

In the Novartis submission, the base case cost-per-QALY for Population1b for Gilenya versus Avonex is £55,634. If the extreme scenario of setting the cost of a relapse to zero is used, then the cost-per-QALY moves from £55,634 per QALY gained to £59,938. See Appendix Analysis 1 for details. This is an increase of £4,304 or 7.7%. There is a wealth of evidence to show that relapses have a substantial cost associated, see Naci 2010 for a recent systematic review[37]. So it is clear that this extreme scenario does not reflect reality. However, the scenario does highlight that even under the most extreme example above the cost of a relapse still has a relatively minor impact on the model. Thus, Novartis recommends that the discussion in the ACD about the selection of the cost of a relapse is removed.

4. The Gilenya serious adverse events (SAEs) were included in the economic model in a systematic manner

Section 3.21 (Page 15) states: “The ERG considered that it was unclear why the costs of only some severe adverse events were included in the model, and why the costs of non-serious adverse events were not included.”

Novartis agrees that an evidence based rule needs to be applied to arbitrate the cut off for including adverse events in the economic model. For this submission Novartis used the rule: “include all of the most serious adverse events listed in the SPC at the time of submission”. Novartis believes this is a reasonable rule to decide which adverse events to include in the model. However, Novartis would have welcomed a discussion with the ERG at the clarification stage about alternative rules.

Regardless of which principles were applied, it is unlikely that there would have been much of an impact given that adverse events/laboratory abnormalities, adverse events leading to drug discontinuation, and serious adverse events were comparable between Gilenya 0.5mg and control. The EMA position was summarised as: “In MS clinical studies, the overall incidence of adverse events and serious adverse events was similar for fingolimod [Gilenya] and matched controls (placebo, interferon beta-1a).”[34] In addition, the comment in **Section 4.5 (Page 23)** of the ACD states: “The Committee understood from the clinical specialists and patient experts that fingolimod [Gilenya] is generally well tolerated and that the adverse events expected during treatment could be managed in routine clinical practice.”

Novartis therefore believes that the discussion in **Section 3.21** about adverse events should be removed because the impact on the cost-per-QALY is limited given that the rate of adverse events is “similar for fingolimod [Gilenya] and matched controls”.

5. Discussion of natalizumab administration cost is not pertinent to this appraisal

Section 3.21 states: “The ERG also raised its concern about potential inaccuracies in the administration costs calculated for natalizumab in the submission. Although natalizumab was not used as a comparator in the model by the manufacturer, the ERG considered that such inaccuracies could limit the potential for an accurate consideration of all the possible alternative treatments.”

The NICE cost template for natalizumab cites tariff code A18 from the 2007/08 tariff as their source for the natalizumab administration cost.[38] In the Novartis submission we intended to use the same tariff code, A18, but use the cost from the latest NHS tariff 2010/2011. However, in the 2010/2011 NHS tariff it is clear that tariff code A18 has been superseded by code AA30Z. This means when a 2010 perspective is taken of the NICE costing template for natalizumab the logical step is to use the equivalent 2010 cost from the 2010/2011 tariff. The 2010/2011 tariff details what cost the NHS will charge for this procedure.

We are open to input from the ERG on this issue, however, we would expect the ERG to provide evidence to support their perspective on the administration cost. Currently the ERG suggests that the administration cost may be inaccurate. During the Novartis systematic review of the literature we did not identify an alternative 2010 UK cost for natalizumab infusions. Therefore, we suggest that given there is no contradictory evidence the sentence should be removed from the ACD.

More importantly however, a disagreement about the correct cost for a treatment does not imply that there must be “inaccuracies” in the other costs; especially when this treatment is not considered in the Novartis economic analysis.

6. The administration costs of Gilenya in the economic model have negligible impact on the cost-per-QALY

Section 3.21 states: “The ERG noted that the administrative and monitoring costs for fingolimod [Gilenya] and Avonex were not adequately justified by the manufacturer. In particular, it was unclear why the manufacturer assumed that patients treated with Avonex would need two more neurology visits in the first year of treatment than patients who received fingolimod [Gilenya].”

This discussion was also repeated in **Sections 4.16 (Page 29)** and **4.17 (Page 30)** of the ACD.

Novartis based the additional requirement for administration and monitoring for the therapy on the Summary of Product Characteristics (SPC) for therapy and the ABN 2009 guidelines for Prescribing in Multiple Sclerosis.

We believe that the administrative and monitoring costs for Gilenya and Avonex are justified. However, we are happy to consider alternative assumptions and would have been happy to discuss these during the ERG clarification questions.

We believe the impact of changing this is very modest. Below is an example where we have assumed six neurology visits for Gilenya in the first year and four for Avonex, see Appendix Analysis 2 for details.

The base case cost-per QALY in the Novartis submission for Population 1b for Gilenya versus Avonex is £55,634 per QALY gained.

When Novartis included six neurology visits for Gilenya in the first year into the model, the cost-per-QALY for Gilenya versus Avonex for Population 1b was increased to £56,534 per QALY gained; an increase of only £900 per QALY or 1.6%.

This demonstrates that the impact of neurology visits has limited impact on the cost-per-QALY. Therefore, Novartis suggests the discussion in the ACD about monitoring costs is removed (**Section 3.21 and Section 4.17).**

In **Section 4.16 (Page 29)** it states that “The Committee also noted that the ERG had identified other minor costing errors in the manufacturer’s model and considered that the revision of these errors was likely to increase the ICER for fingolimod [Gilenya].”

Novartis can find no details in the ERG report about what these “other minor costing errors” are. In the absence of any detail or information from the ERG, Novartis suggests that this discussion is also removed.

7. Use of trial utility data in the economic model

Section 3.24 (Page 16) states that the ERG cautioned that published utility data had been used in the model instead of the EQ5D data from the trials. This is also repeated in **Section 4.12 (Page 27)** and in the summary **Section 4.17 (Page 30)**.

In the Markov model 20 health states are described (RRMS EDSS 0 to 9, and SPMS EDSS 0 to 9).

The Novartis systematic review identified four potential utility sources for MS by EDSS (see Table 59 of the submission). These studies were Parkin 1998, Orme 2007, Biogen 2007 study, and the utilities reported by ScHARR in NICE TA 32.

- Parkin 1998 was rejected because it only reports utilities for five of the 20 health states in the model.
- The Orme 2007 study and the Biogen 2007 study is the same data set but with different methods of combining the EDSS half states (0.5, 1.5, 2.5 etc). The differences in the reported utility between the Orme 2007 and Biogen 2007 are small.
- The utilities reported by ScHARR in TA 32 are not described in any detail which raised some substantial doubt about the credibility of the values. For instance the patient sample size was not reported, and the tool and methodology used to determine the utility score is not stated. These values are reproduced in TA 127.

Orme 2007 was selected because it presented utility scores for all 20 states and the description of the study methodology had been peer reviewed.

As discussed at the Appraisal Committee Meeting and in our response to the ERG report the trial utility data was not selected because there is only data available for seven of the 20 health states (RRMS EDSS 0 to 6). So the other 13 states would need to be populated with data from the literature. Novartis felt our approach fits with the latest NICE methods guide and is more conservative.

The ERG criticised the choice of Orme 2007 because there are negative utility values for EDSS 8 and 9. A negative value simply means that the patient views this state as worse than death. It is worth noting that in all the studies which measured utility for EDSS state 9 they report a negative utility value. This includes the utility data the ERG prefers from the ScHARR model report for NICE TA 32. EDSS state 8 is described as “Essentially restricted to bed, chair, or wheelchair, but may be out of bed much of day; retains self care functions, generally effective use of arms”.[39] EDSS state 9 is described as “Helpless bed patient, can communicate and eat”. Based on the results of the Orme 2007 study, the 181 UK subjects in these two states did view the two states as essentially worse than death.

Novartis therefore, believes the criticism about negative utilities by the ERG should be removed from the ACD.

Section 3.24 of the ACD then goes on to state: “The ERG suggested that since the manufacturer’s base case targeted very specific patients (population 1b), it would have been more appropriate to use utility data for these patients, which were available directly from the trials.” This is also repeated in **Section 4.12 (Page 28).**

As stated above, utility data is available from the two Gilenya Phase III trials FREEDOMS and TRANSFORMS. But these trials had the entry criteria of RRMS and EDSS 0 to 5.5 so utility data is only available for seven of the 20 health states.

The ERG suggested in their report that Novartis use the Gilenya trial data for the seven health states where it is available and then use the literature to populate the remaining 13 states. It is not obvious to Novartis that it is a conservative assumption to combine utility data in this manner. However, below is an analysis where the trial utility data is used for RRMS EDSS 0 to 6, and the Orme 2007 data is used in the remaining 13 states, see Appendix Analysis 3 for details.

In the Novartis submission the base case cost-per QALY for Population 1b for Gilenya versus Avonex was £55,634 per QALY gained. This used Orme 2007 utility data for all 20 health states.

When Novartis substituted the FREEDOMS utility values into the model for RRMS EDSS 0 to 6, the cost-per-QALY for Gilenya versus Avonex for Population 1b was **reduced** to £52,982 per QALY gained.

When Novartis substituted the TRANSFORMS utility values into the model for RRMS EDSS 0 to 6, the cost-per-QALY for Gilenya versus Avonex for Population 1b was **reduced** to £52,866 per QALY gained.

This demonstrates that Novartis has been conservative by not using the utility data from the Gilenya clinical trials in the base case analysis. In addition, as can be seen above the impact of using the utility data is modest. Therefore, it is unclear to Novartis why the ERG and NICE are strongly questioning why Novartis did not use the clinical trial utility data.

Section 3.24 (Page 17) of the ACD describes how the ERG combined the utility data from ScHARR in TA 32 for EDSS scores 7 to 10 instead of Orme 2007.

As described above, the methodology of obtaining these utility scores in TA 32 is not described. However, the Orme 2007 study is peer reviewed and in the publication it details the methodology of collection via EQ-5D from 2048 UK subjects in 2005. Novartis questions why the ACD asserts it is more robust to substitute the published Orme 2007 utility data with the unpublished data from TA 32.

Novartis suggests that the discussion about the clinical trial utility data in the model has been overstated by the ERG and NICE, and so Novartis suggests that **Section 3.24** is changed to (underlining indicates the suggested change):

> "The ERG stated that the manufacturer had chosen external literature in favour of the trial outcomes to derive utility data. The ERG suggested that since the manufacturer's base case targeted very specific patients (population 1b), it would have been more appropriate to use utility data for these patients, which were available directly from the trials. However, when the baseline utility reported in the FREEDOMS and TRANSFORMS trials were substituted into the model it was found that the cost-per-QALY decreased slightly in favour of fingolimod."

Novartis also suggests that **Sections 4.12** and **4.17** are changed along the same lines since the use of the utility data from the clinical trials does not lead to uncertainty in the model results.

8. Use of trial data to inform EDSS distribution model cohort

Section 3.25 states "The ERG expressed concern regarding the representativeness of the initial EDSS score distribution used in the model."

Novartis carried out a systematic review to identify potential sources for the EDSS distribution. This identified three sources: London Ontario, the UK RSS, and the UK MS

survey data. The drawback is that they are all for a general RRMS population and not Population 1b specifically.

So when Novartis modelled Population 1b (the base case) we used the EDSS distribution from the pooled TRANSFORMS and FREEDOMS dataset for the subgroup Population 1b. There is a typographical error in the submission in Section 6.3.1 which contradicts this. Novartis apologises for any inconvenience caused by this error.

When Novartis modelled Population "1b but not 2", we used the EDSS distribution from the pooled TRANSFORMS and FREEDOMS dataset for the subgroup Population "1b but not 2".

Novartis believed it to be more robust and fitting with the NICE reference case to use data specifically for Population 1b in the base case, where available, since this would match the population being modelled.

In the ERG report the ERG state: "...the trial samples (used further in the model) may not be representative of the nonresponder population within routine clinical practice."

There is no data published for the EDSS distribution for Population 1b, so it is unclear what information the ERG is basing this assessment on. The ERG appears to have taken the view that the distribution used in the Novartis model is doubtful.

During the five day fact check of the ERG report Novartis highlighted this concern and the ERG responded with: "The ERG has not made any claims on what is or is not correct to use in the model; specifically, the ERG has not stated that the EDSS distributions used in the model are inappropriate."

It is not clear to Novartis that **Section 3.25** of the ACD reflects this response from the ERG. We suggest the sentence discussing the EDSS distribution is removed from the ACD.

In addition, it is worth comparing this situation for EDSS distribution with the situation for the utility data. For the utility data the ERG has taken the view that Randomised Control Trial (RCT) data is more appropriate. But for the EDSS distribution the use of RCT data has been criticised. Novartis believes that NICE prefers RCT data where it is available. However, the ACD is inconsistent about whether RCT data is more appropriate or not.

9. Use of relative risks in the model

In **Section 3.23 (Page 15 and 16)** the ERG expresses concern about the use of relative risk (RR) and suggests hazard ratios (HR) should have been used instead.

The use of HR measures of relative treatment effect are suited in comparing the outcomes over time in the form of 'survival' curves, and in estimating new outcome curves for additional treatments (based on a comparator's known outcome curves). For this economic analysis, we were dealing with transition probabilities at fixed follow-up points in time – expressed as a probability of moving from one health state to another health state. In such cases a RR approach would seem appropriate and in line with previous technology appraisals, where models have generated efficacy data employing a common comparator and indirect analysis using measures of RR. For instance, in the NICE STA for natalizumab RR were used and this was not specifically criticised. The model used in the Gilenya NICE STA is identical in this regard to the natalizumab model.

Using the RRs did at times generate values in the probabilistic sensitivity analysis (PSA) which would cause adjusted transition probabilities to fall outside of the 0-1 boundary. A fix was implemented in the model preventing the generation of transition probabilities outside of the 0-1 boundary. HRs are bound by the same rules as RRs (i.e., they can be less than and greater than unity – for smaller or larger effect sizes). Therefore, when adjusting underlying natural history transitions there is nothing to distinguish between HR and RR that would stop absolute adjusted transition rates exceeding 1 (when samples come at high HR values).

In the ERG report in Table 34 (Page 99) the ERG quote the following HR for disease progression reproduced in Table 6 below.

Table 6: Hazard Ratios (HR) for disease progression from the ERG report

	Population 1b	**Population 1b but not 2**
	(95% confidence interval)	(95% confidence interval)
Avonex vs. Placebo	[redacted]	[redacted]
Gilenya vs. Placebo	[redacted]	[redacted]

Highlighting indicates Academic-in-confidence

The base case cost-per QALY in the Novartis submission for Population 1b for Gilenya versus Avonex is £55,634 per QALY gained.

When Novartis substituted the above HR into the model the cost-per-QALY for Gilenya versus Avonex for Population 1b was **reduced** to £52,906 per QALY gained. See Appendix Analysis 4 for details.

The base case cost-per QALY in the Novartis submission for Population "1b but not 2" for Gilenya versus Avonex is £18,741 per QALY gained.

When Novartis substituted the above HR into the model the cost-per-QALY for Gilenya versus Avonex for Population "1b but not 2" was **reduced** to £18,725 per QALY gained.

Substituting HR as suggested by the ERG rather than RR in the model produced slightly more favourable results. This means the analysis in the Novartis submission was conservative towards Gilenya. This point was raised at the Appraisal Committee Meeting but the ACD does not reflect this.

Therefore, Novartis believes this entire discussion about HR in **Section 3.23** is both unnecessary and misleading. We suggest that **Section 3.23** is removed from the ACD.

10. Novartis model incorporates both relapse risk and disease progression

Section 3.27 (Page 19) it discuses that the "...the ERG cautioned that the impact of disease-modifying therapy could be double-counted in the model."

The original model was built by the NICE assessment group ScHARR to inform the NICE appraisal of the cost effectiveness of beta interferons and glatiramer acetate (NICE TA 32 2002). In addition, the same model was used in the NICE STA of natalizumab and this was accepted by the ERG at that time (TA 127 2007).

Novartis believes this assumption is generally conservative against the more effective treatment. Gilenya has been proven to improve annualised relapse rate and disability progression. In addition, TRANSFORMS has demonstrated that Gilenya improves relapse rate and disease progression greater than Avonex so the impact of the assumption will be more conservative against Gilenya than Avonex. Therefore, we believe the comment in **Section 3.27** should be removed.

11. The adverse event macular oedema is included in the Novartis analysis

Section 4.5 includes a discussion about macular oedema. In the Gilenya SPC it recommends monitoring for macular oedema and this resource cost is included in the economic model. In addition, the economic model includes the disutility due to macular oedema. The objective of this discussion in **Section 4.5** is unclear to Novartis and it is worth reflecting that during the clinical trial programme only two cases of macular oedema was reported at the licensed dose of 0.5mg and that both of the cases of macular oedema improved or resolved after study drug discontinuation.[40] Cases reported at the higher unlicensed dose of 1.25mg (n=14) also resolved or improved after study drug discontinuation except two cases complicated by concomitant baseline cicatricial retinitis and optic neuritis. Thus Novartis believes this sentence about macular oedema should be removed from the ACD.

In summary, Novartis believes the submission was robust because:

- The data was selected in a systematic manner and better dialogue at the ERG clarification stage would have demonstrated this
- The inclusion of adverse events was undertaken in a systematic manner.
- The effect of using Hazard Ratios as advised by the ERG would make Gilenya more cost effective, i.e. **reduce the cost-per-QALY**
- The impact of different assumption of the monitoring costs has **negligible impact on the cost-per-QALY**
- Using the utility data (EQ5D) from the trials as advised by the ERG would make Gilenya more cost effective, i.e. **reduce the cost-per-QALY**

Therefore, Novartis believes the discussion of these various points within the ACD should be revised or removed.

Appendix

In the response Novartis have undertaken some additional simple analysis with the model to support our response. Below is a description of what changes were made to the submitted model for each analysis.

Analysis 1: The cost of relapse used in the model has limited impact on the cost-per-QALY

For this analysis we changed Cell G24 from £3039 to zero in the 'Disease Costs' sheet of the model.

Analysis 2: The administration costs of Gilenya in the economic model have negligible impact on the cost-per-QALY

For this analysis we changed Cell F16 from 2 to 6 in the 'Admin Costs' sheet of the model.

Analysis 3: Use of trial utility data in the economic model

a) FREEDOMS

For this analysis we changed (Cells D13:J13) to the FREEDOMS utility which was provided to the ERG during the clarification questions. Details of each change is below in the table

EDSS state	Changed from	Changed to
0	0.870	0.90
1	0.799	0.88
2	0.705	0.83
3	0.574	0.74
4	0.610	0.67
5	0.518	0.65
6	0.460	0.54

b) TRANSFORMS

For this analysis we changed (Cells D13:J13) to the TRANSFORMS utility which was provided to the ERG during the clarification questions. Details of each change is below in the table

EDSS state	Changed from	Changed to
0	0.870	0.89
1	0.799	0.86
2	0.705	0.85
3	0.574	0.77
4	0.610	0.71
5	0.518	0.63
6	0.460	0.55

Analysis 4: Use of relative risks in the model

a) Population 1b (Highlighting indicates Academic-in-confidence)

For this analysis we changed Cell E16 from [redacted] to [redacted] and Cell E22 from [redacted] to [redacted] in the 'Efficacy' sheet of the model.

a) Population "1b but not 2"

Please note: for this analysis only we have used the version of the model which was sent to NICE on the 13th May 2011 during the ERG clarification questions. This version of the model had been revised to model "Population 1b but not 2".

For this analysis we changed Cell E18 from 1.274 to 1.209 and Cell E22 from 0.579 to 0.520 in the 'Efficacy' sheet of the model.

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