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5th January 2012

Dear Professor Longson

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

Thank you for your letter dated 24th November 2011 inviting comments on the above.

Novartis is disappointed that the Committee has not recommended fingolimod at this stage. However, we are encouraged that the Committee has recognised the clinical effectiveness and innovation of fingolimod. There is a clear unmet medical need for people with highly active RRMS who continue to relapse, despite first-line therapy with medications that require injections. We are confident that fingolimod will address this need and that fingolimod is cost-effective in this patient population.

We note the changes to this second ACD (ACD2) compared to the first ACD (ACD1) circulated for comments in August 2011. We agree with many of the changes and believe some of the interpretations of the evidence are more appropriate. However, we remain convinced that some of the summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence provided. Therefore, we do not think that this provisional recommendation is sound. In particular we would like to discuss the following three points:

A. We support the discussion about innovation and value beyond the QALY, and we would like to highlight a few further points that were not considered in Section 4.20 of the ACD2.
B. The assumption by the Committee that one third of first line injection sub-optimal responder patients receive best supportive care (BSC) in the UK is not supported by the available evidence and clinical opinion
C. A maximum level of 5% BSC in the mix of comparators reflects the UK clinical evidence. This results in a cost effectiveness of £27,820 per QALY.

These points are discussed within Sections A, B and C of our response.

We have updated the economic model assumptions to match changes requested by the Committee. Please see section D of our response, where this new base case cost-effectiveness is presented following your request in Section 4.18 of the ACD2.

We also note the request in Section 4.18 to investigate the directional effect of changing the natural history and this is discussed in Section E of our response.

We sincerely encourage the Committee to reconsider its draft guidance in light of our comments and those of the wider MS community, especially the wealth of feedback sent in from healthcare professionals to ACD1. We believe that our response addresses the overall comment from the Committee relating to uncertainties regarding the cost effectiveness of fingolimod.

The maximum level of BSC in this patient population is 5%, or less, as supported by a wealth of clinical evidence and real world experience. This brings the cost effectiveness of fingolimod versus a mix of comparators to £27,820 per QALY, which is under the £30,000 threshold.

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

Yours sincerely

[redacted]

This appraisal is focused on the cost-effectiveness of fingolimod in relapsing remitting multiple sclerosis (RRMS) patients with high disease activity despite prior treatment with a beta-interferon. These patients are defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year (Population 1b).

A. We agree that the ICER has not adequately captured the value and innovative nature of fingolimod.

Novartis supports and welcomes the discussion in Sections 4.19 and 4.20 that fingolimod is a valuable new oral therapy, with a novel mode of action, which has additional benefits not captured in the QALY assessment. In addition, we agree with the Committee that including these factors in the model would decrease the ICER.

Novartis would like to highlight that in the two previous NICE appraisals of MS therapies, the positive recommendations have been based on base-case ICERs higher than the £30,000 threshold. In TA127 the base-case ICER of £32,000 for natalizumab versus beta interferon was used for the positive recommendation in Rapidly Evolving Severe (RES). Following an initial negative TA32 the positive recommendation for the beta interferons in RRMS from the MS Risk Sharing Scheme was based on the ICER of £36,000. This allowance was due to the acknowledgment of a number of "special factors" which might be considered relevant to the cost effectiveness of treatments for MS.[1] These factors were:

i. the impact of treatment on the severity (independent of the frequency) of relapses, and
ii. possible cost offsets from the avoidance of severe levels of disability requiring intervention by the Personal Social Services.

In regard to point (i) fingolimod has been shown to reduce the number of severe relapses and relapses affecting patients' daily activities compared with interferon beta-1a or placebo.[2] Moreover, compared with interferon beta-1a (im*) or placebo, fingolimod significantly reduced the Annualised Relapse Rate (ARR) for relapses from which there was an incomplete recovery. The severity of relapse and incomplete recovery were not included in the cost effectiveness analysis. Had these factors been incorporated, the ICER would certainly be lower.

In regard to point (ii) the NICE reference case details which costs should be included in the cost-effectiveness analysis. This means costs such as informal care are not included. Several studies have shown that between 62% and 76% of UK people with MS rely upon informal care provided by friends and family.[3,4,5] This informal care saves the Department of Health (DoH) money that it would otherwise have to spend. Fingolimod is more effective at reducing relapses and disease progression compared to existing MS therapies.[6] So it is reasonable to assume that the need for informal care is decreased with fingolimod compared to existing therapies such as interferon beta-1a. If the care was provided by the DoH then the cost would have appeared in the cost-effectiveness model and would have contributed to the ICER for fingolimod being lower. Therefore, we suggest when the Committee considers the ICER for fingolimod, it should remember that the real ICER will be lower because of this decreased need for informal care.

* im, intramuscular

We note that Section 4.2 of the ACD2 states "[t]he Committee also heard from the patient experts that fingolimod would allow greater flexibility". This point is further elaborated in the submissions of evidence from both the MS Society and the MS Trusts.[7,8] They both clearly state that injections have a significant impact on the lifestyle of people with MS. Injections and infusions limit people's ability to travel and disrupt their daily life. Fingolimod is an oral formulation and so avoids the need for these injections or infusions. The disutility of injection site reactions is included in the economic model, but capturing the disruption to a person's life is far harder to capture in the QALY. Therefore, if the benefit of the oral formulation was completely captured in the QALY it would result in the ICER being lower.

Finally, the DoH maintains that the ICER of £36,000 for the beta interferon "provides patients with access to the drugs at a price which makes them cost effective" and this sentiment is reflected in a recent statement from the DoH about the MS Risk Sharing Scheme (RSS) issued in December 2011.[9] This appraisal of fingolimod has taken into account the prices of the interferon beta preparations specified in the MS RSS. As discussed in Section C, this results in a cost effectiveness of fingolimod versus a mix of comparators of £27,820 per QALY.

B. The assumption by the Committee that one third of sub-optimal responder patients receive BSC is not supported by the available evidence and clinical opinion

Section 4.18 of the ACD2 states that the Committee believes that fingolimod should be compared to a weighted mean of BSC and a mix of beta-interferons.

The Committee also stated in Section 4.18 that the proportion receiving best supportive care (BSC) would be one-third.

UK clinical consensus, audits from UK MS centres, and UK market share data does not support this. The clinical evidence clearly shows that the maximum proportion being managed by BSC in this patient population would be no more than 5%.

The clinical consensus does not support the assumption that one third of patients with a sub-optimal response to their first beta interferon will move to BSC. During the consultation on ACD1, over 50 UK expert MS clinicians confirmed that withdrawing beta interferon treatment for patients with a sub-optimal response to their first beta interferon was not clinically rational and did not reflect clinical practice.

Stakeholder and public comments received in response to ACD1 unanimously support the view that BSC is not the appropriate comparator. The consensus view from both consultant neurologists and nurses was that no patient failing on first-line treatment would be taken off active treatment and managed with BSC in the UK.

> *"no patient in the UK with continuing relapses (failing interferon treatment) is treated with best supportive care." (consultant neurologist via NICE website)*
>
> *"[BSC]...simply does not reflect the clinical practice and the standard of care provided in the UK". (NHS professional via NICE website)*
>
> *"best supportive care....does not reflect the standard of care provided in the UK". (Letter from a consultant neurologist at Kings Neuroscience centre)*

Finally, Novartis does not recall a clinical discussion at the second Appraisal Committee Meeting (ACM) in October that would have resulted in a consensus that one third of patients with a sub-optimal response to their first beta interferon would receive BSC. This view is highlighted in Section 4.3 of the ACD2 which states that "clinicians are generally reluctant to stop treatment altogether after a suboptimal response". Our records also highlight that the clinical expert opinion did not support BSC.

We believe that the assumption of one third relates to the proportion of treatment naive RRMS patients receiving BSC. This is not the same population for which fingolimod is being appraised which is sub-optimal responders to prior beta interferon therapy (Population 1b). It is important not to confuse these populations. We are unconvinced that sub-optimal responders patients would be relegated to BSC. As discussed above, our view is supported by the wealth of expert evidence received during the ACD1 consultation.

In addition, after receiving the ACD2 Novartis has contacted three MS units and their feedback does not support the belief that one third of patients having a sub-optimal response to their first beta interferon would receive BSC. Their feedback is summarised below. The mean level of BSC across these three sites is 3.9%.

Addenbrookes hospital, Cambridge
Their figures for 2011 are that fewer than 3% of new DMT patients ceased treatment and went on to BSC.

North Midlands MS Service
In RRMS patients "NONE of our patients who fail treatment go onto BSC as if they are continuing to relapse we need to continue with treatment of one form or another."

Salford MS centre
Since 1996, they have started 1,180 patients on one of the DMTs covered by the MS Risk Sharing Scheme. Of these, 103 (8.7%) stopped active therapy due to a perceived lack of efficacy.

An independent clinical practice patient registry was accessed in December 2011. [10] The registry contained 86 UK RRMS patients who had a relapse despite being managed with a disease modifying therapy (DMT). The registry confirmed that in the 12 months after the relapse only 6% cease DMT therapy.

Market research data also does not support the assumption that a third of UK patients failing on an interferon will move to BSC. In one retrospective analysis of 102 UK RRMS patients who have been receiving treatment within the last year and have experienced one or more relapses in the last year, only 7% discontinue DMT therapy.[11] Similarly, Adelphi market research data of 88 UK RRMS patients initiated onto a DMT has shown that within six months only one subject (1%) had stopped therapy.[12]

Given that switching to a different beta interferon in patients with a sub-optimal response to their first beta interferon is routine clinical practice in the UK, and has been associated with enhanced efficacy, Novartis maintains that active treatment remains the only appropriate comparator and not BSC.

In addition, all of the UK data presented above casts doubt on the assumption that a third of patients having a sub-optimal response to the first beta-interferon would receive BSC. The mean level of BSC presented in this Section is 4.3% and so the maximum proportion would be less than 5%.

C.The impact of reflecting the available evidence which supports a proportion of less than 5% of patients being managed by BSC

Section 4.18 of the ACD2 states that the Committee believes the comparator for fingolimod should be a mix of beta interferon and best supportive care (BSC). The Committee believes that the proportion being managed with BSC would be one third.

As discussed in Section B of this response, UK clinical consensus, audits from UK MS centres, and UK market share data does not support this belief that a third would be managed by BSC.

Based on clinical audits, clinical experience and market research a more appropriate proportion of BSC for patients with highly active RRMS not responding to their first interferon beta is, at the most, 5%.

When the cost-effectiveness analysis is run using the requested updated model (see Section D of this response) with 5% being managed with BSC, it results in an incremental cost effectiveness ratio (ICER) versus fingolimod of £27,820. This is clearly beneath the upper cost-effectiveness threshold of £30,000 and demonstrates that fingolimod is indeed cost-effective.

As discussed in Section B, UK clinical consensus, audits from UK MS centres, and UK market share data does not support the belief that a third of patients with a sub-optimal response to a beta interferon would be managed by BSC. The available evidence strongly indicates that a more appropriate proportion of BSC would not exceed 5%. To maintain the remaining part of the weighted mean the proportions of the beta interferons interferon beta-1a (sc), interferon beta-1a (im), and interferon beta-1b reflect the proportions as per the Prescriptions Pricing Authority (PPA) proportions in Table 1.

Table 1 Prescriptions Pricing Authority (PPA) proportions of interferon beta preparations from Jan 2008 to June 2010

Therapy	Patient share
Interferon-beta-1a im (Avonex)	43%
Interferon-beta-1a sc (Rebif)	36%
Interferon-beta-1b (Betaferon and Extavia)	21%
Total	100%

im intramuscular, sc subcutaneous

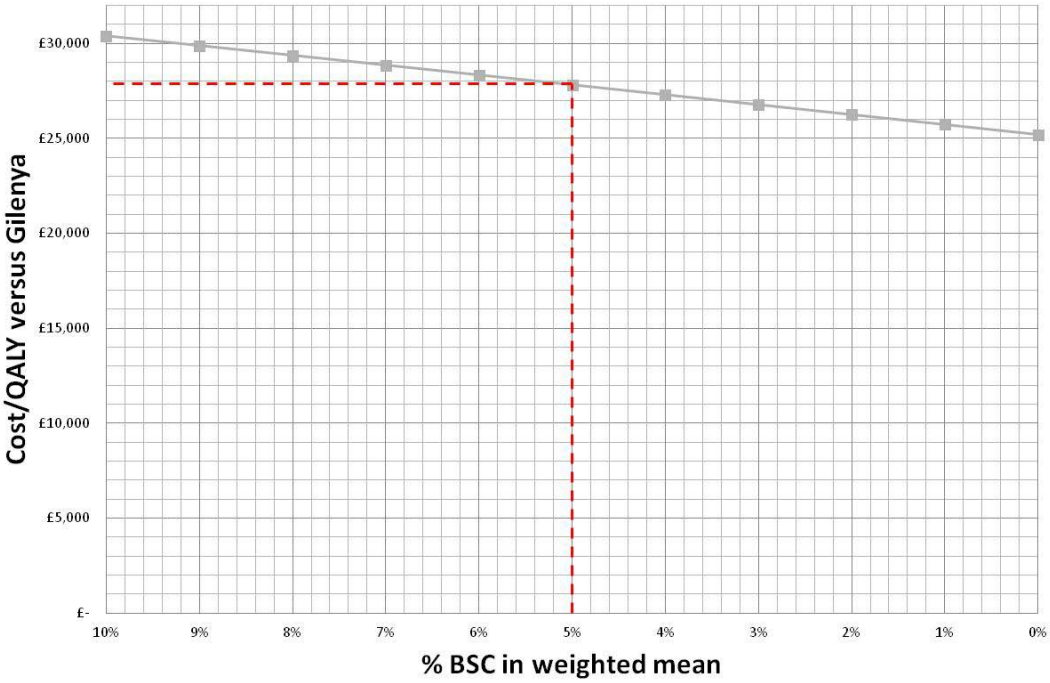
This results in composition of the mix of comparators as shown in Table 2. When this analysis is run using the updated model described in Section D, it results in a ICER versus fingolimod of £27,820.

Table 2 Composition of the mix of comparators

Therapy	Patient share
Best Supportive Care	5.00%
Interferon-beta-1a im (Avonex)	40.80%
Interferon-beta-1a sc (Rebif)	34.28%
Interferon-beta-1b (Betaferon and Extavia)	19.92%
Total	100.00%

The impact of varying the proportion of BSC across the range of the reported levels of BSC (0% to 8.7%) is presented in Figure 1. The composition of the mix of comparators maintained the proportions of interferon beta preparations from the PPA. At all points between 0% and 8.7% the ICER versus fingolimod is less than £30,000. Based on the discussion in Section B above we are positive that the proportion of Population 1b receiving BSC is lower than 5%. This means that we are confident that the ICER of fingolimod versus an evidenced-based mix of BSC and beta interferon is less than £30,000.

Figure 1. Impact of varying the proportion of BSC in the weighted mean composed of BSC and all the beta interferons (updated model with PAS).



D.Updated base case cost-effectiveness analysis

As requested in section 4.18 of the ACD2 we have updated the economic model assumptions to match the changes requested by the Committee. In summary we have incorporated the trial EQ5D for EDSS 0 to 6, and added the assumption that there is a 50% waning after 5 years. For completeness we have also updated the administration costs of fingolimod, and the comparators to reflect the discussion in Section 4.16.

These results are presented below and we have sent NICE the updated model incorporating these changes. The specific implementation of these changes into the economic model are reported in detail in Appendix 1.

There is no data to suggest a waning effect with fingolimod and data exists to the contrary. Data for fingolimod in extension phases of both Phase 2 and Phase 3 studies suggests efficacy is maintained to four years and beyond. The concept of waning efficacy is also without precedent in prior MS NICE appraisals. However, as can be seen in the discussion below the impact of the 50% waning is minimal.

In summary, the impact of updating the model as requested in ACD2 increases the ICER fingolimod versus interferon beta-1a (im) by £1,450.

Base case: fingolimod vs. interferon beta-1a (im) [Avonex] comparison for Population 1b

Section 4.18 requests that a probabilistic analysis is preferred by the Committee for this comparison. The point estimate of 5000 iterations of the model is presented in Table 3 for fingolimod versus interferon beta-1a (im) in patients with a sub-optimal response to a beta interferon (Population 1b).

In the fingolimod patient access scheme (PAS) application form, which used the original model, the point estimate of 5000 iterations of the model was an ICER of £15,825 for fingolimod versus interferon beta-1a (im). Therefore, the impact of updating the model as requested in ACD2 increases the ICER by £1,450.

Table 3 Probabilistic base-case results (updated model with the PAS)

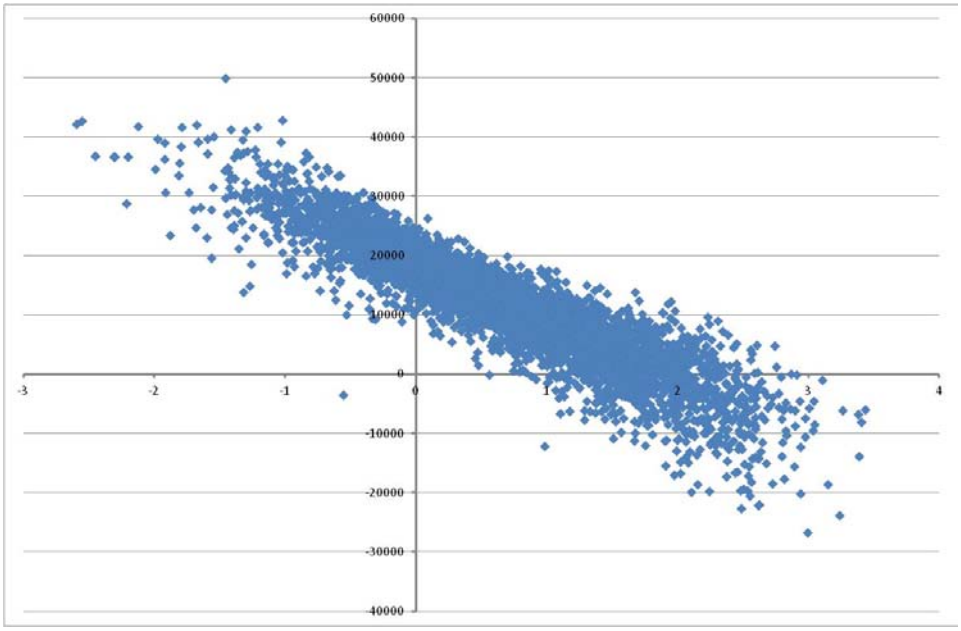
	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Interferon beta-1a (im)	£271,322	3.779			
Fingolimod	£283,076	4.459			
Fingolimod vs. Interferon beta-1a (im)	-	-	£11,754	0.680	**£17,275**

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years; im intramuscular. PAS, patient access scheme.

Figure 2 shows incremental costs and effect pairs for each of the 5000 iterations of the probabilistic sensitivity analysis (PSA). The figure shows that for the vast majority (77%) of iterations of the PSA fingolimod is more effective than interferon beta-1a

(im). We can also see that in 11% of iterations fingolimod is both more effective and less costly than interferon beta-1a (im).

Figure 2. PSA scatter plot of fingolimod vs. interferon beta-1a (im) (updated model with PAS)



Interferon beta-1a (sc) [Rebif-44] comparison for Population 1b

In the Novartis response to ACD1 we provided an analysis of fingolimod versus interferon beta-1a (sc) in Population 1b. This analysis was based on the analysis presented in the ERG report where the ERG undertook an analysis of the cost-effectiveness of fingolimod versus interferon beta-1a (sc) (Pages 103 to 104). Novartis is cautious about this analysis because it uses efficacy data from EVIDENCE which is a study in first-line RRMS patients, and not patients with a suboptimal response to a previous interferon beta (Population 1b). Appendix 2 details how the original model was updated to incorporate this comparison. The 95% confidence intervals (CI) were not available in the ERG report but we have also calculated these so that the model can now run the preferred probabilistic analysis.

Table 4 presents the updated probabilistic ICER of £30,936 for fingolimod versus interferon beta-1a (sc).

In the PAS application form, which used the original model, the deterministic ICER was £27,774 for fingolimod versus interferon beta-1a (sc) in Population 1b with the PAS. Therefore, the impact of updating the model as suggested in ACD2 and using a probabilistic analysis is to increase the ICER by £3,162.

The main caveat of this comparison is that the efficacy data for interferon beta-1a (sc) is for RRMS patients and not those patients with a suboptimal response to a previous interferon beta (Population 1b). This means the efficacy data used in this analysis is likely to over estimate the efficacy of interferon beta-1a (sc). Consequently the cost effectiveness analysis shown in Table 4 is likely to under estimate the cost effectiveness, i.e. in reality the cost per QALY for fingolimod versus interferon beta-1a (sc) in Population 1b will be lower than £30,936.

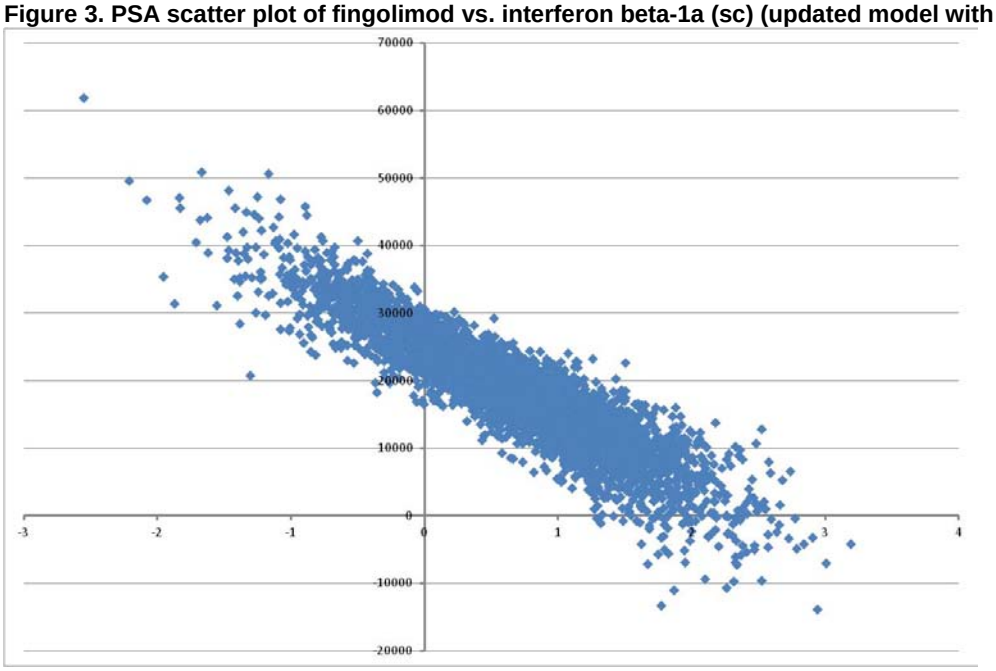
Table 4 Interferon beta-1a (sc) exploratory analysis (updated model with the PAS)

	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Interferon beta-1a (sc)	£264,852	3.862			
Fingolimod	£283,927	4.479			
Fingolimod vs. interferon beta-1a (sc)			£19,076	0.617	£30,936

sc, subcutaneous

Figure 3 shows incremental costs and effect pairs for each of the 5000 iterations of the probabilistic sensitivity analysis (PSA). We can see from the figure that for the vast majority (82%) of iterations of the PSA fingolimod is more effective than interferon beta-1a (sc).

Figure 3. PSA scatter plot of fingolimod vs. interferon beta-1a (sc) (updated model with PAS)



Exploration of the weighted mean using a mixture of all the beta interferons and BSC

In Section 4.18 of ACD2 it states “The Committee therefore considered that best supportive care should be included as a comparator, together with a mix of beta interferons (with the proportions for the beta interferons determined based on market share data from the Prescriptions Pricing Authority).” This composition is summarised in Table 5. Please note that the breakdown of the two strengths of interferon beta-1a (sc) (Rebif-44 and Rebif-22) is not available. The most conservative estimate, that is the least favourable to fingolimod, is to assume that all of the interferon beta-1a (sc) patients received Rebif-44. Betaferon and Extavia are the same molecule, interferon beta-1b, sold under different brand names. The patient share of Extavia is less than 1% so it is combined with Betaferon.

Table 5 Composition of the mix of comparators outlined in ACD2

Therapy	Patient share
Best Supportive Care	33.33%
Interferon-beta-1a im (Avonex)	28.63%
Interferon-beta-1a sc (Rebif)	24.06%
Interferon-beta-1b (Betaferon and Extavia)	13.98%
Total	100.00%

im intramuscular, sc subcutaneous

To complete this analysis efficacy data is required for the beta interferons in Population 1b, that is the population where patients are having a sub-optimal response to a previous beta interferon. The Novartis systematic review has identified efficacy data for interferon beta-1a (im) and fingolimod only. However, there is no data for either interferon beta-1a (sc) or interferon beta-1b. As discussed above, an indirect analysis has been used to estimate the efficacy of Interferon beta-1a (sc). In the Novartis PAS application we suggested a method to estimate the efficacy of interferon beta-1b was to scale the Novartis mixed treatment comparison (MTC) results. For the purposes of this exploratory analysis we have followed the same methodology for interferon beta-1b, see Appendix 2 for details.

As discussed in Section C, the evidence base clearly shows that no more than 5% of patients having a sub-optimal response to a beta interferon would be managed with BSC. In Table 6 we have summarised this comparison of fingolimod versus a weighted comparator composed of 5% BSC and the beta interferons interferon beta-1a (im), interferon beta-1a (sc) and interferon beta-1b. As can be seen this results in an ICER of £7,820.

Table 6 Weighted mean ICER versus all beta interferons (updated model with the PAS)

	Share of weighted mean	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs (£)	ICER
BSC	5.00%	£11,198	0.181			
Interferon beta-1a (im)	40.80%	£110,701	1.542			
Interferon beta-1a (sc)	34.28%	£90,797	1.324			
Interferon beta-1b	19.92%	£50,258	0.689			
Weighted mean		**£262,954**	**3.736**			
Fingolimod		£283,076	4.459			
Fingolimod vs. weighted mean	-	-	-	£20,122	0.723	**£27,820**

<u>50% waning after five years over estimates the impact of therapy waning</u>

Section 4.18 of ACD2 asserts that incorporating a waning effect of 50% after five years is more plausible. This effect has been incorporated into the updated model, however, we believe the 50% waning after five years vastly overstates any potential treatment waning.

There is no evidence that supports the hypothesis that the efficacy of fingolimod will reduce by 50% after five years. In the Novartis submission we presented five-year data at the higher dose of 1.25 mg fingolimod which demonstrated that the efficacy of fingolimod is maintained for five years.[13] The ARR for patients randomized to fingolimod was 0.31 to 0.37 during year 1 and for the two dose groups and was 0.13 to 0.18 during the fifth year of therapy. Likewise the mean T1 Gd-enhancing lesion count for the 1.25mg and 5mg dose groups were 1.0 and 0.2 respectively Month 12 and 0.2 and 0.1 respectively at Month 60 (at which time all patients were on 1.25mg). These data argue against any loss of efficacy over time in those who remain on therapy.

Since the fingolimod submission, the two year extension to the two year FREEDOMS (fingolimod versus placebo) study has completed.[14] The study is still being written up and only a preliminary analysis is available as academic-in-confidence. [redacted]

We also believe the degree of assumed efficacy reduction of 50% after five years is biologically implausible. Fingolimod is not a biologic medicine and thus would not

elicit immunogenicity that could reduce efficacy over time unlike neutralizing antibodies that form against the beta interferons and natalizumab in approximately 10 to 40% of patients over time. It is worth considering that in both TA32 (beta interferons) and TA127 (natalizumab) there was no requirement to include a treatment waning effect in the economic modelling. In both of these appraisals the treatment effect of all the beta interferons and natalizumab were maintained throughout the lifetime of the model which was over 20 years.

No data exist to support loss of efficacy of fingolimod over time and uncontrolled data that does exist argues strongly against waning efficacy for periods of at least 4-5 years. If one did incorporate a waning effect in the model, as outlined in Section 4.18 of the ACD2 such a change has a limited impact on the cost effectiveness analysis of fingolimod.

Novartis maintains the view that using interferon beta-1a (im) as a representative for the entire beta interferon class is appropriate. The direct comparative data of fingolimod versus interferon beta-1a (im) from TRANSFORMS provides a valid and clinically relevant comparator. Using interferon beta-1a (im) as the comparator corresponds to an ICER of £17,275 using the updated model (Table 3). In the PAS submission which used the original model, the probabilistic analysis demonstrated an ICER of £15,825 for fingolimod versus interferon beta-1a (im). So the impact of the updated model increases the ICER by £1,450 per QALY.

If a mix of comparators is used with the updated model the result is an ICER of fingolimod versus the mix of £27,820 per QALY (Table 8).

E. Directional effect of changing the natural history matrix

As requested in Section 4.18 of the ACD2, below is an exploration into the directional effect on the ICER of using alternative assumptions on natural history disability progression.

In Section 4.15 of the ACD2 the clinical specialist queried that the natural history matrix used to describe the progression of MS patients may allow more rapid disability progression than seen in the UK MS clinics. In response to this there are three points that Novartis would like to raise.

1) All previous reported UK cost-effectiveness models used the London Ontario data set as reference, similar to the fingolimod submission

2) The suggestion that MS is now progressing more slowly than previously thought may represent a change in the type of patient with MS being seen in MS clinics and clinical trials today. The London Ontario population was regionally based (and thus comprehensive) and untreated, representing the natural history of the disease. Perceived slower progression currently may reflect a less representative population or, optimistically, the impact of therapies on disease course. This does not reduce the relevance of the natural history data derived in London Ontario.

3) This submission is focused on a population with a sub optimal response to their first beta interferon. These are high disease activity patients who are still relapsing despite prior treatment. Given the relationship of relapses to disability progression,[15, 16, 17, 18,19] this is a patient population that will progress more rapidly than the treatment naive RRMS patient. This is supported by a comment in response to the ACD1 from an NHS professional that "Progression of disability in these patients is approximately twice as fast as in patients with less active multiple sclerosis".

In order to answer the request in Section 4.18 of ACD2 to investigate the potential effect of changing the natural history dataset to slow disability progression we have considered this encompasses two factors:

i. the proportion of subjects in the matrix progressing each year
ii. the number of EDSS states a subject can progress each year.

With reference to point (i) Novartis does not believe that the proportion of subjects in the matrix is progressing faster than would be expected in this population. The clinical data for fingolimod supports this view. By two years in the placebo arm (i.e. no active treatment) of FREEDOMS, 23% of patients progressed in the subgroup of high disease activity patients who are still relapsing despite prior treatment (Population 1b). In the model in the untreated population, 22% of patients progressed by two years.

Since the clinical data supports the proportions that are progressing in the model we see no need to further investigate this factor.

With reference to point (ii) within both FREEDOMS and TRANSFORMS the greatest disability progression was three EDSS states within a 12-month period. If the

extreme assumption of preventing the subjects in the model from moving more than one RRMS EDSS state a year is used, this has the impact of increasing the ICER for fingolimod versus interferon beta-1a (im) from £13,553 to £17,229 if a deterministic analysis is undertaken. The point estimate from 5000 iterations of the probabilistic analysis is an ICER of £21,244 for fingolimod versus interferon beta-1a (im). This is an increase of £3,969 from the base case probabilistic ICER of £17,275. See Appendix 3 for further details.

If the same extreme assumption of preventing the subjects in the model from moving more than one SPMS EDSS state a year is also used, this has the impact of changing the ICER for fingolimod versus interferon beta-1a to £16,187 if a deterministic analysis is undertaken, or £19,774 if the probabilistic analysis is run. In this analysis both RRMS and SPMS progression in the natural history matrices are limited to progression of one EDSS state at a time.

Limiting the model to allow a subject to change by only one EDSS state at a time per year is an extreme assumption and does not reflect the clinical data for this population.

Any analysis on the directional effect of changing the natural history matrix needs to reflect the points made above that the population being appraised is a population with a sub optimal response to their first beta interferon. These are high disease activity patients who are still relapsing despite prior interferon beta treatment. By definition, this is a patient population who will see more rapid disease progression than the treatment naive RRMS patient. The discussion presented here demonstrates that the matrix in the model is reasonable for this particular population and drastically slowing down the progression of the model cohort has a marginal negative impact on the ICER.

Summary of the cost-effectiveness analysis presented by Novartis

- In the original economic model, the probabilistic ICER in patients with a sub-optimal response to a beta-interferon (Population 1b) for fingolimod versus interferon beta-1a (im) [Avonex] was £15,825 (See Patient Access Scheme application form for details).

- The impact of updating the model as requested in ACD2 increases this ICER by £1,450 to £17,275 (Table 3, Section D). The updated model incorporates the trial utility data, 50% waning effect, and the updated fingolimod administration costs.

- Exploring the directional effect on the ICER by using the alternative assumption that subjects can only progress one RRMS EDSS state a year results in an ICER of £21,244 versus interferon beta-1a (im) (Section E).

- Exploring the directional effect on the ICER by using the alternative assumption that subjects can only progress one RRMS or one SPMS EDSS state a year results in an ICER of £19,774 versus interferon beta-1a (im) (Section E).

- If a mix of comparators is used (including 5% BSC) as requested in ACD2 it results in an ICER of £27,820 per QALY using the updated model (Table 6, Section D).

- All of these ICERs are beneath the upper cost-effectiveness threshold of £30,000 and so demonstrates that fingolimod is cost-effective in patients with a sub-optimal response to a beta-interferon (Population 1b).

In conclusion, the Committee has accepted the clinical effectiveness and innovation of fingolimod in patients who have had a suboptimal response to a beta interferon. Novartis are convinced fingolimod will help to relieve the burden of current unmet medical need in this patient population. The updated model has an ICER of fingolimod versus interferon beta-1a (im) of £17,275 per QALY. Alternatively if a mix of comparators is used, then the clinical evidence supports a maximum of 5% BSC, and this is associated with an ICER of £27,820 per QALY.

Appendix 1- Revised model

The updated model has been revised to incorporate the following three items.

1. Incorporating trial utility data in the economic model

The FREEDOMS and TRANSFORMS utility data were provided to the ERG during the clarification questions. The values are very similar and the impact on the ICER of using either FREEDOMS or TRANSFORMS in the model is £23 per QALY. Therefore, we have applied the mean utility for each EDSS state.

EDSS state	FREEDOMS	TRANSFORMS	Mean of FREEDOMS and TRANSFORMS
0	0.900	0.890	0.895
1	0.880	0.860	0.870
2	0.830	0.850	0.840
3	0.740	0.770	0.755
4	0.670	0.710	0.690
5	0.650	0.630	0.640
6	0.540	0.550	0.545

In the model we changed (Cells D13:J13) to the mean utility for each EDSS state. Details of each change are below in the table.

EDSS state	Value in original model	Changed to
0	0.870	0.895
1	0.799	0.870
2	0.705	0.840
3	0.574	0.755
4	0.610	0.690
5	0.518	0.640
6	0.460	0.545

2. Incorporating 50% waning of treatment effect at 5-years

Cell E29 of the “settings” sheet is a switch which allows the waning effect to be incorporated. The switch has been selected. Cell E31 has been set to “5” years, cell E32 set to “45” years, and cell E35 set to “50%”

3. Revised administration costs

As detailed in Section 4.16 of the ACD2 we have revised the model so that people receiving fingolimod would have three hospital visits during the first year compared with two visits for people receiving interferon beta-1a.

Cell F16 of the “admin” sheet has been changed from 2 to 3
Cell F59 (interferon beta-1a sc) and Cell F77 (interferon beta-1a im) have been changed from 4 to 2

Appendix 2

Interferon beta-1a (sc) comparison

In the ERG analysis an indirect comparison (Bucher et al., 1997) was applied to the results reported from the EVIDENCE trial in conjunction with results from the FREEDOMS and TRANSFORMS trials to derive relative risks of progression and relapse for interferon beta-1a (sc) as compared to best supportive care (BSC). These results are reported in Table 39 Page 103 of the ERG report.

In the updated model Cell E17 of the "efficacy" sheet was changed to 0.753 to incorporate the relative risk of disability progression of interferon beta-1a (sc) versus placebo. Cell E52 was changed to 0.785 to incorporate the relative risk of relapse of Interferon beta-1a (sc) versus placebo.

In order to run the preferred probabilistic analysis we have calculated the 95% Confidence Intervals (CI). The lower CI for relative risk of progression 0.252 was entered into Cell F17 of the "efficacy" sheet and the upper CI of 2.252 was entered into Cell G17. The lower CI for relative risk of relapse of 0.467 was entered into Cell F52 and the upper CI of 1.317 was entered into Cell G52.

In the ERG report the withdrawal rate for interferon beta-1a (sc) is not specified, so in the PAS application Novartis has used the withdrawal rate from the EVIDENCE publication. So Cell E79-E88 was changed to 16/339=0.0467.

Interferon beta-1b (Betaferon/Extavia) comparison

In the PAS application we scaled the RRMS MTC efficacy to reflect that the therapy is being considered in patients with a sub-optimal response to a previous beta interferon (Population 1b) and not the RRMS population. The selection of the scale factor of 13.25% is based on the observation that 13.25% scales both the interferon beta-1a MTC endpoint of relative risk of relapse and relative risk of progression to be approximately equal to the result from the indirect comparison of interferon beta-1a versus fingolimod in the Population 1b. Therefore we assume that interferon beta-1b will experience a reduction in efficacy in Population 1b similar to the reduction observed for interferon beta-1a.

As discussed in the PAS application template, we believe this is a reasonable estimate since 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.[20,21,22,23] In addition, as part of the NICE MTA of DMTs the assessment group concluded that the clinical trials do not suggest major differences in the efficacy of different preparations of beta interferon.[24]

In the updated model Cell E19 of the "efficacy" sheet was changed to [redacted] to incorporate the relative risk of disability progression interferon beta-1b versus placebo. Cell E54 was changed to [redacted] to incorporate the relative risk of relapse of interferon beta-1b versus placebo.

For the discontinuations we have not adjusted the MTC result. Intuitively in the sub optimal population you would expect the discontinuation rate to increase compared with RRMS which would reduce the ICER for Gilenya. In the absence of robust evidence that the discontinuations do increase, we have chosen the conservative assumption of not adjusting the discontinuation rates. Cells G79 to G88 have been changed to [redacted]

Appendix 3 – Methods to investigate the directional effect of changing the natural history matrix

The RRMS natural history transition matrix in the model is shown in Table 7**.** It is in the model on sheet 'Natural history transition' in Cells D248 to N258. The analysis here focuses firstly on the RRMS matrix and then we will consider the impact of also slowing the SPMS progression matrix in the same manner.

Table 7. RRMS Natural history transition matrix in model (Academic in confidence)

From EDSS/ to EDSS	0	1	2	3	4	5	6	7	8	9	10
0	[redacted]										
1	[redacted]										
2	[redacted]										
3	[redacted]										
4	[redacted]										
5	[redacted]										
6	[redacted]										
7	[redacted]										
8	[redacted]										
9	[redacted]										
10	[redacted]										

Limiting the maximum number of EDSS states a subject can progress each year to 1 in the RRMS matrix

To undertake this analysis the probability of staying in the same EDSS state was kept constant. However, the probability of progressing one EDSS equalled the probability of moving to any other RRMS EDSS in the base care matrix. For instance, Cell D248 of the base case matrix has a probability of [redacted] to stay in RRMS EDSS 0, see Table 7. The probability to moving to a higher RRMS EDSS state (1 to 10) equals the sum of Cells E248 to N248 of the base case matrix which is [redacted]. So in the matrix exploring what happens if progression by only one EDSS

state is allowed, Cell E248 would now equal [redacted], see Table 8. The remaining EDSS states F248 to N248 are set to 0. This calculation is undertaken for the rest of the table, see Table 8 for summary.

Table 8. Matrix where only one EDSS state transition is possible for RRMS. (Academic in confidence)

From EDSS/ to EDSS	0	1	2	3	4	5	6	7	8	9	10
0	[redacted]										
1	[redacted]										
2	[redacted]										
3	[redacted]										
4	[redacted]										
5	[redacted]										
6	[redacted]										
7	[redacted]										
8	[redacted]										
9	[redacted]										
10	[redacted]										

<u>Adding in the maximum number of EDSS states a subject can progress each year to 1 in the SPMS matrix</u>

Similar to the RRMS discussion above the probability of staying in the same SPMS EDSS state was kept constant. However, the probability of progressing one SPMS EDSS equalled the probability of moving to any other SPMS EDSS in the matrix. For instance, Cell V130 of the SPMS matrix has a probability of [redacted] to stay in SPMS EDSS 2, see Table 9 . The probability to moving to a higher SPMS EDSS state (3 to 10) equals the sum of Cells W130 to AD130 of the matrix which is [redacted]. So in the matrix exploring what happens if progression by only one EDSS state is allowed, Cell W130 would now equal [redacted], see Table 10. The remaining EDSS states X130 to AD130 are set to 0. This calculation is undertaken for the rest of the table, see Table 10 for a summary.

Table 9. SPMS Natural history transition matrix in model (Academic in confidence)

From EDSS/ to EDSS	0	1	2	3	4	5	6	7	8	9	10
0	[redacted]										
1	[redacted]										
2	[redacted]										
3	[redacted]										
4	[redacted]										
5	[redacted]										
6	[redacted]										
7	[redacted]										
8	[redacted]										
9	[redacted]										
10	[redacted]										

Table 10. Matrix where only one EDSS state transition is possible for SPMS (Academic in confidence)

From EDSS/ to EDSS	0	1	2	3	4	5	6	7	8	9	10
0	[redacted]										
1	[redacted]										
2	[redacted]										
3	[redacted]										
4	[redacted]										
5	[redacted]										
6	[redacted]										
7	[redacted]										
8	[redacted]										
9	[redacted]										
10	[redacted]										

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