NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Fingolimod for the treatment of relapsing-remitting multiple sclerosis

Response to consultee, commentator and public comments on the second Appraisal Consultation Document (ACD2)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
MS Society	The MS Society welcomes the opportunity to resolve any outstanding issues regarding this appraisal. However, we remain conscious of the time period it will now take NICE to arrive at a final decision regarding this treatment option. We would like to remind NICE that by the time a final decision has been made this particular treatment will have been licensed for 13 months. We request that NICE do not make this process any more drawn out and lengthy than it needs to be. We sincerely hope that after such extensive consultation, this appraisal will conclude with a positive outcome for people with MS. We refer NICE to our previous submissions for further detail. Our key remaining concerns are as follows: 1. It is not clear what evidence has been used to support the assumption that one third of people with relapsing and remitting MS who have a sub-optimal response to beta-interferons will receive best supportive care. This seems to be in contrast to the views of clinical specialists. 2. There is no evidence to support the claim that there is a waning of treatment efficacy in Fingolimod yet the cost-effective analysis by the Evidence Review Group (ERG) presents a reduction in efficacy over time. This is in contrast to the two year trial data which showed no reduction in efficacy. 3. The recommendation not to prescribe Fingolimod on the NHS condemns a group of people with no treatment option to progressive disability and higher relapse rates. For those who have not responded to first line treatments, but who are unable to take Tysabri due to risks of progressive multifocal leukoencephalopathy (PML), there is no alternative treatment.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The Committee heard from the manufacturer that there is currently no evidence to support the hypothesis that the efficacy of fingolimod will reduce over time and preliminary results from the FREEDOMS extension study show that there is no loss of efficacy over 4 years. In the absence of data beyond 4 years, the Committee decided to be cautious and assume a 50% waning of treatment effect after 5 years in the base-case analysis. However, it acknowledged that if the treatment effect did not wane over time then this would overestimate the base case ICER (FAD section 4.13).

Consultee	Comment	Response
MS Society	**Sub-optimal responses** The ACD refers to the ERG's estimation that approximately one-third of people with relapsing and remitting MS have sub-optimal response to beta-interferon treatment and will receive best supportive care. This assumes that they would not try an alternative beta-interferon or choose to try Tysabri. It is not clear what data or evidence has been used to support the claim that one-third receive best supportive care and yet it appears to be central in the rationale for using best supportive care as a comparator. We would like to see evidence upon which this claim is substantiated and call upon the ERG to present their evidence base for this claim. It is our understanding that this estimation is in contrast with the views of clinical specialists as evidenced by initial research led by Dr Eli Silber and a group of neurologists and MS nurses. Only 4.9 per cent of respondents said that they would stop therapy and offer best supportive care following a relapse whilst on a first line injectable disease modifying treatment.	Comments noted. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The manufacturer's revised analysis submitted in response to the second appraisal consultation document compares fingolimod with a weighted average of beta interferons and best supportive care to reflect the current variation in clinical practice to manage RRMS. Best supportive care only represents 5% of this comparator, in line with clinical opinion.
MS Society	**Optimism versus conservatism** We are greatly concerned that an overly cautious approach has been taken in the production of this second ACD using questionable evidence. The waning of the treatment effect, whilst not proven, is incorporated into the model. The model considers reduction of effect yet there is little explanation of what this is based on. The ERG must provide further explanation of the rationale to explain what evidence there is to suggest that the effects of Fingolimod will reduce over time. We would like to see the evidence used to support this claim such as evidence to suggest if there are any signs that there might be a reduced effect over a longer period of time. Other DMDs have shown that their effects continued for over 10 years. Evidence to show why it is suggested that the effects of Fingolimod would reduce would be welcome. Following our submission in August we are pleased to see that the Committee has placed a greater emphasis on the innovation that this treatment offers; the reduction in relapses and the reduced side effects. However, we are disappointed that these have not been weighted to their full impact and that the overall impact of having MS is still described as having a 'substantial negative impact on quality of life and activities of daily living'. This condition does not have merely a 'negative impact', it is life altering; MS changes the lives of individuals, couples and families.	Comments noted. The Committee noted that sensitivity analyses carried out by the manufacturer and the ERG showed that a reduction in the assumed duration of treatment effect increased the ICERs substantively. The Committee heard from the manufacturer that there is currently no evidence to support the hypothesis that the efficacy of fingolimod will reduce over time and preliminary results from the FREEDOMS extension study show that there is no loss of efficacy over 4 years. In the absence of data beyond 4 years, the Committee decided to be cautious and include a 50% waning of treatment effect after 5 years in the base-case analysis. However, it acknowledged that if of the treatment effect did not wane over time then this would overestimate the base case ICER (FAD section 4.13). Section 4.2 of the FAD has been updated to highlight that multiple sclerosis is a life altering

Consultee	Comment	Response
	This treatment provides a highly innovative method of application with reduced side effects and offers a much higher reduction in relapses than current first line therapies. Whilst the ACD acknowledges this it does not incorporate it into the model. There are numerous examples where we read that a positive impact has not been considered as it was not possible to establish the exact effect, whereas, possible negative impacts are incorporated into the model. There is concern that this has resulted in an imbalanced pessimistic approach rather than balancing possible negative effects with possible positive impacts.	condition. The Committee discussed the innovative nature of fingolimod and whether the assessment of the change in health-related quality of life had been inadequately captured in the economic analysis. It heard from the patient experts that people who receive fingolimod have fewer adverse reactions than those who receive beta-interferon therapy. In addition, treatment with fingolimod significantly reduces relapses and could allow people to lead an active and fulfilling life and contribute more fully to society. The Committee also heard from the manufacturer that any impact of treatment with fingolimod on the severity of relapses had not been captured in the model. The Committee accepted that fingolimod is a valuable new therapy and that its oral formulation represents innovation in the treatment of multiple sclerosis. The Committee recognised that including all of the benefits suggested by the manufacturer and patient experts in the manufacturer's model could decrease the ICER to a level that would be considered a cost-effective use of NHS resources (FAD section 4.19).
MS Society	**Equality concerns and discrimination** We are greatly concerned that there is an equality issue that is not being addressed. The place of Fingolimod in the treatment pathway is unique. It provides a new and innovative treatment for a group of people who have previously been left without a treatment option. It fulfils an unmet treatment need. For people with MS who are not responding to beta-interferons, but due to risk of PML are not able or willing to be treated with Tysabri, Fingolimod offers an important treatment option. There is an unmet need for treatment in this particular group and Fingolimod could provide the first treatment available for people with MS who, to date, have no effective treatment options. Previously this group has been left with one of three options. Firstly, to continue on their current treatment path but with reduced impact; secondly, to be treated with Tysabri despite the risk of PML; or thirdly to give up all treatment options and follow the	Comments noted. The Committee accepted that fingolimod is a valuable new therapy and that its oral formulation represents innovation in the treatment of multiple sclerosis (FAD section 4.19). The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access

Consultee	Comment	Response
	best supportive care route accepting that this will lead to a possible increase in relapses and ultimately, disability progression. The survey results presented by the neurologists show that for those who fulfil the criteria for Tysabri none would consider stopping therapy; 11.6 per cent would consider escalating to fingolimod; 8.9 per cent would consider changing to another DMT; and 78.6 per cent would chose escalating to a monoclonal antibody therapy. It is inappropriate to compare Fingolimod with no treatment. People with MS who do not show optimum efficacy on treatments will ordinarily try alternatives and remain on some form of treatment as they would rather be on a treatment, even if it has reduced impact, than no treatment at all. This is a shared view between the MS Society and clinical specialists and is supported by recent survey results which show best supportive care as an option considered by neurologists only once relapse and remitting MS has progressed to secondary progressive MS. To compare costs of an effective treatment against costs of best supportive care, i.e. no treatment, which puts people on a path of continual disease progression, is highly questionable. To choose to allow a group of people to face increasing disability when they might otherwise be treated and have reduced disability and relapses for some years could be viewed as discriminatory. Individuals with more active forms of MS should not be excluded from treatment options. Best supportive care is an inappropriate comparator for this new and novel treatment for all the reasons highlighted in previous submissions. As supported by recent evidence from neurologists and MS nurses, best supportive care is a last resort when there are no viable options and when relapse and remitting MS has progressed to secondary progressive MS. Best supportive care is an inappropriate comparator for relapse and remitting MS treatments. It does not reflect current UK clinical practice or professional guidelines. Comparing a treatment with no treatment removes the ability to capture reduced relapse rates and relative benefits of a reduced propensity to suffer side effects. The use of best supportive care has previously been discounted as a comparator (TA 127) and therefore we are concerned that there is an inconsistent and unfair approach in appraisals.	scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The manufacturer's revised analysis submitted in response to the second appraisal consultation document compares fingolimod with a weighted average of beta interferons and best supportive care to reflect the current variation in clinical practice to manage RRMS. Best supportive care only represents 5% of this comparator, in line with clinical opinion.
MS Society	**Concluding Remarks** We encourage NICE to share the evidence which states that one third of people with relapsing remitting MS who have a sub-optimal response to beta-interferons will receive best supportive care. It is important to understand on what basis best	Comments noted. The manufacturer's response to the second appraisal consultation document highlights that 1/3 of treatment-naïve patients with RRMS may receive best supportive care, however

Consultee	Comment	Response
	supportive care has been chosen as an appropriate comparator. We also encourage NICE to share the evidence which supports the suggestion that the efficacy of fingolimod will wane. It is important to understand the assumptions used in the ERG's cost-benefit analysis. We hope that NICE will include the evidence of the survey results presented by Dr Eli Silber and colleagues in their consideration of fingolimod and consider the place of fingolimod in the treatment pathway. It is clear that the confusion around the place of fingolimod in the treatment pathway underlines the need to produce a comprehensive prescribing pathway for use in treating people with MS. This also supports the need to fully update the clinical guideline for MS in a truly comprehensive manner which includes all treatments for MS. We hope that NICE will receive our comments in the constructive manner that they are intended. We urge NICE to continue to work with the Department of Health and the pharmaceutical company to try to find a way forward in order to provide a previously untreated group with an effective treatment option.	this is a different population to that considered in this appraisal, (that is, those who have had a suboptimal response to previous therapy).The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The Committee noted that sensitivity analyses carried out by the manufacturer and the ERG showed that a reduction in the assumed duration of treatment effect increased the ICERs substantively. In the absence of data beyond 4 years, the Committee decided to be cautious and include a 50% waning of treatment effect after 5 years in the base-case analysis. However, it acknowledged that if of the treatment effect did not wane over time then this would overestimate the base case ICER (FAD section 4.13). The Committee also emphasised that it is important that a new model for multiple sclerosis is developed for any future appraisals of treatments for multiple sclerosis. The new model should ideally be based on UK patient cohorts, should use the best available evidence (including experience to date from the risk-sharing scheme) and should include all currently available treatments, so that future appraisals of treatments for multiple sclerosis are directly relevant to UK clinical practice (FAD section 4.20).
MS Trust	The MS Trust maintains that fingolimod is an important additional treatment for people with highly active relapsing-remitting multiple sclerosis. Disease burden varies between individuals and it is important to recognise that	Comments noted. Clinical specialists were present at the first two Committee meetings and a number of written responses from clinical professionals and their professional organisations

Consultee	Comment	Response
	people with MS being considered for treatment with fingolimod have experienced a significant number of relapses. The case regarding best practice in management of those with highly active disease must be made based on their needs and not on those elsewhere on the disease spectrum. We have previously noted our concern about the absence of committee members with expertise in neurology. Our view is that this is undesirable and disadvantages the review process, particularly with regard to a complex condition such as MS. A greater involvement from clinicians with specialist neurological expertise in MS throughout the review process would have avoided errors in understanding of current management of relapsing-remitting MS. While we recognise that clinical experts were present at Committee meetings, we continue to believe that this was insufficient input to ensure that all relevant clinical issues were identified and the clinical context adequately described.	were received during the course of the appraisal, which were considered by the Committee.
MS Trust	Research evidence demonstrates the importance of active, early treatment of relapsing-remitting MS to prevent axonal damage and avoid irreversible disability. The EMA has licensed fingolimod because it is an effective, safe drug for people with MS who have very few available treatment options. The difficulty in calculating cost effectiveness of MS drugs is well recognised, particularly as the trial data does not address the long-term benefits of treatment. People with MS in the UK are at risk of lagging even further behind other developed countries in their access to licensed drugs. The MS Trust encourages the Committee to recognise that fingolimod would be an important addition to the small range of available disease modifying therapies for MS and should be made available to those with sub-optimal response to first line therapies. Best supportive care should not be seen as a desirable clinical alternative in highly active relapsing-remitting MS, unless it is the patient's consistently expressed preference. As with other disease modifying therapies, fingolimod should be prescribed by neurologists, with commencement of therapy and ongoing monitoring provided by MS nurses.	Comments noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
MS Trust	It is regrettable that there is no opportunity to consider fingolimod with respect to natalizumab. The exclusion of those with rapidly evolving severe disease is unfortunate and neglects a group for whom fingolimod may provide a significant treatment option.	Comments noted. The Committee heard from the clinical specialists that fingolimod would provide the greatest benefit to people with rapidly evolving severe relapsing–remitting multiple sclerosis, because they currently have very few treatment

Consultee	Comment	Response
	The Committee has rejected the manufacturer's use of Avonex only as the base-case comparator. The Committee has used a comparator composed of equal portions of best supportive care, Rebif-44 and Avonex. The MS Trust challenges this assertion. It is important to note that best supportive care means no disease modifying treatment whatsoever. Research evidence supports the treatment of people with relapsing-remitting MS early in the disease to prevent axonal damage and irreversible disability. There is evidence that in the target group for whom there is marketing authorisation for fingolimod, progression of disease is likely to be twice as fast as in those with less active disease. Current practice in the management of relapsing-remitting MS is active and acknowledges that even if people with MS continue to have relapses whilst on disease modifying therapy, they may still be deriving clinical benefit from the treatment.	options. The Committee acknowledged the clinical specialists' disappointment that a specific recommendation for the use of fingolimod in this population could not be made because the manufacturer had not submitted an analysis of fingolimod compared with natalizumab in this population (FAD section 4.4). The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The manufacturer's revised analysis submitted in response to the second appraisal consultation document compares fingolimod with a weighted average of beta interferons and best supportive care to reflect the current variation in clinical practice to manage RRMS. Best supportive care only represents 5% of this comparator, in line with clinical opinion.
MS Trust	The Committee has inconsistently applied its understanding of current clinical practice to its deliberations. The Committee acknowledges that clinicians would be very reluctant to stop treatment (4.3), yet applies a comparator which is composed of 1/3 best supportive care (4.18). The alternative comparator does not realistically reflect clinical practice in the management of relapsing-remitting MS, particularly with respect to the proportion of patients it suggests are receiving best supportive care. The reality in clinical practice is more complex than is represented in the ACD. Patients with a sub-optimal response to a disease modifying treatment may be offered another first-line therapy or switched to natalizumab. Best supportive care is the least desirable and least common option, reserved largely for when all disease modifying treatments are poorly tolerated or the person with MS has expressed a strong and enduring preference for no treatment.	Comments noted. The manufacturer's response to the second appraisal consultation document highlights that 1/3 of treatment-naïve patients with RRMS may receive best supportive care, however this is a different population to that considered in this appraisal, (that is, those who have had a suboptimal response to previous therapy).The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3).

Consultee	Comment	Response
MS Trust	Given the rapid developments in this treatment area the MS Trust would recommend an earlier date for review of fingolimod for highly active relapsing-remitting MS.	Comment noted. A review will only be undertaken if new evidence becomes available which is likely to impact on the final recommendations in the published guidance.
MS Trust Endorsed by several UK consultant neurologists	Fingolimod for the treatment of relapsing remitting multiple sclerosis (RRMS) – Second Appraisal Consultation Document We are writing as a group of specialist consultant neurologists with a particular interest in MS. We were concerned to learn that the second NICE ACD for fingolimod included opinion regarding the management of MS patients failing on therapy that we believe does not reflect clinical practice in the UK. We do not agree that 33% of patients failing treatment on their first injectable disease modifying therapy (DMT) would be offered what was termed "best supportive care" as a treatment option and there is little evidence in clinical practice to support this. We therefore developed a brief online survey to try and ascertain in the short time available a better picture of broad UK clinical practice when treating patients with relapsing remitting MS (RRMS) who fail on their first injectable DMT. The survey was initially sent to consultant neurologists in the UK of which 43 replied. The MS Trust and UK MS specialist nursing association UK MSSNA) also requested that the survey was sent to MS Specialist Nurses who have close contact with patients and play a key role in identifying treatment failures and managing patients when changing therapy. 73 specialist MS Nurses responded to the questionnaire (please note question 1 was added following the request from the MS Trust and UK MSSNA, by which time 41 consultant neurologists had already replied). This survey was developed to respond rapidly within the short NICE consultation period and as such has some possible weaknesses. It does not necessarily include all MS specialist neurologists in the UK and the scenarios presented were intentionally limited. However, we believe that the 116 responses received are broadly reflective of MS clinical practice within the UK and form a valuable body of opinion that should be considered during the NICE appraisal of fingolimod. Results from survey responses: In the question designed to illustrate a relapsing remitting MS patient (RRMS)	Comments noted. The manufacturer's response to the second appraisal consultation document highlights that 1/3 of treatment-naïve patients with RRMS may receive best supportive care, however this is a different population to that considered in this appraisal, (that is, those who have had a suboptimal response to previous therapy).The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The Committee heard from the clinical specialists that treatment of relapsing–remitting multiple sclerosis is determined by the severity of the disease. The Committee heard from the clinical specialists that after a suboptimal response to the first disease-modifying treatment used, clinicians are likely either to offer a different beta interferon or glatiramer acetate, or offer the patient a higher dose of beta interferon (such as Rebif-44). The Committee also heard that clinicians are generally reluctant to stop treatment altogether after a suboptimal response (FAD section 4.3). The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous

Consultee	Comment	Response
	who fulfils the treatment criteria for Natalizumab (Question 2) • The vast majority of responses (77.6%) chose escalating to a monoclonal antibody therapy as their preferred management option for this type of patient • 9.5% would consider changing to another injectable DMT therapy • 12.1% would consider escalating to fingolimod • 0% would consider stopping therapy and providing Best Supportive Care When asked about a patient on a first-line disease modifying therapy who fulfils the treatment criteria for fingolimod (on an injectable DMT with one severe relapse within the last year) (Question 3) • 30.2% of respondents would continue current interferon injectable first line therapy • 9.5% would change to another injectable DMT therapy • 36.2% would escalate to monoclonal antibody therapy (out of licence) • 23.3% would consider fingolimod • Only one respondent would consider stopping therapy and providing Best Supportive Care When asked about a patient with relapsing remitting MS patient (RRMS) on a first-line injectable DMT who has had a recent relapse (potentially fulfilling fingolimod criteria) (Question 5) • 60.7% recommended remaining on current therapy • 18.5% would change to a second injectable first line DMT therapy • 5.6% would offer a drug trial • 15.9% would escalate therapy • Of note only 4.9% would stop therapy and offer Best Supportive Care When presented with a clear case of secondary progressive Multiple Sclerosis (SPMS) which is out of licence for monoclonal antibody therapy and fingolimod (Question 6) • 48.7% would continue current injectable DMT therapy • 32.2% would stop therapy and provide Best Supportive Care Question 4 asked respondents about their perception of treatment failure. Respondents were able to identify more than one criterion • 86.1% felt that two significant relapses in the last year constituted treatment failure	treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.

Consultee	Comment	Response
	• 60% felt that new active lesions on MRI constituted treatment failure • 40.1% felt that one significant relapse in the last year constituted treatment failure • Of note 67% felt that patients that cannot tolerate injections or side effects also constituted treatment failure In conclusion, we believe that this data from neurologists with a special interest in MS and MS specialist nurses suggests: 1. There is general agreement about what constitutes treatment failure. There is a sizeable group (40.1%) that consider one significant relapse in the last year as a treatment failure 2. It is standard practice within the UK to change to a more potent therapy if there is failure on first-line injectable disease modifying therapy o Despite the fact that fingolimod has recently been licensed, that funding remains uncertain and there is little clinical experience in the UK, many colleagues consider fingolimod to be a valid treatment option for patients failing on first line injectable DMT therapy 3. The overwhelming majority of respondents would not consider stopping therapy for patients with relapsing remitting MS (RRMS) who have relapsed on first line injectable DMT therapy and offer "Best Supportive Care" as an option o There is clear opinion on where Best Supportive Care is a valid option, this is where a patient has clear Secondary Progressive MS (SPMS) for which fingolimod is not licensed o Less than 5% of respondents considered Best Supportive Care to be the best option for a relapsing remitting MS (RRMS) patient with a breakthrough relapse We would strongly urge NICE to reconsider this second draft guidance and recommend fingolimod for use in patients with active disease who fulfil the prescribing criteria.	
North Yorkshire and York Primary Care Trust	The commissioning of neurology services is carried out by Yorkshire & Humber Specialist Commissioning Group which also includes policies relating to drug treatments for multiple sclerosis. The present policy can be found on their website: http://www.yhscg.nhs.uk/Downloads/Policy/DMT%20criteria.doc. This includes the prescribing criteria for beta interferon, glatiramir acetate and natalizumab.	Comments noted. The Committee heard from the clinical specialists that fingolimod would provide the greatest benefit to people with rapidly evolving severe relapsing–remitting multiple sclerosis, because they currently have very few treatment options. The Committee acknowledged the clinical specialists' disappointment that a specific

Consultee	Comment	Response
	These are the comments provided by NHS North Yorkshire and York for the above ACD. • **Has all of the relevant evidence been taken into account?** Yes. • **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, but it is unfortunate that the manufacturer could not provide evidence to allow a comparison to Natalizumab for patients with rapidly evolving severe relapsing remitting multiple sclerosis. It would have been useful to evaluate the clinical and cost effectiveness of fingolimod in this cohort of patients. • **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Yes.	recommendation for the use of fingolimod in this population could not be made because the manufacturer had not submitted an analysis of fingolimod compared with natalizumab in this population (FAD section 4.4). The Committee debated the difficult position it had been placed in, requiring it to make a decision on the use of fingolimod compared with treatments which are not recommended by NICE but widely used within the NHS. The Committee acknowledged that the ICERs for fingolimod fell within a range which would be considered an acceptable use of NHS resources after ignoring that the comparators were previously deemed not cost effective by NICE. However, the Committee noted that the current risk-sharing scheme allows beta interferons to be purchased at a price which the Department of Health considers to be a cost-effective use of NHS resources; but outcome data from the scheme to justify the negotiated procurement price for these treatments are lacking. Taking these difficulties into consideration, the Committee made an exceptional case and recommended fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults on if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (population 1b from the manufacturer's submission). See FAD section 4.20.
Novartis Pharmaceuticals UK	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-	The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous

Consultee	Comment	Response
	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. 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.	treatment with beta interferon (that is, population 1b from the manufacturer's base case) and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information. Responses to issues relating to points A, B, C and D are below. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The manufacturer's revised analysis submitted in response to the second appraisal consultation document compares fingolimod with a weighted average of beta interferons and best supportive care to reflect the current variation in clinical practice to manage RRMS. Best supportive care only represents 5% of this comparator, in line with clinical opinion. The Committee concluded that the most plausible ICER for fingolimod compared with the weighted average of the comparators was likely to be in the range of £25,000 to £35,000 per QALY gained (FAD section 4.17). The Committee recognised that including all of the benefits suggested by the manufacturer and patient experts which may not have been adequately captured in the QALY calculation in the manufacturer's model could decrease the ICER to a level that would be considered a cost-

Consultee	Comment	Response
		effective use of NHS resources (FAD section 4.19).
Novartis Pharmaceuticals UK	**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. 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. Moreover, compared with interferon beta-1a (intramuscular) 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.This informal care saves the Department of Health (DoH) money that it	Comments noted. The Committee discussed whether the assessment of the change in health-related quality of life had been inadequately captured in the economic analysis. It heard from the patient experts that people who receive fingolimod have fewer adverse reactions than those who receive beta-interferon therapy. In addition, treatment with fingolimod significantly reduces relapses and could allow people to lead an active and fulfilling life and contribute more fully to society. The Committee also heard from the manufacturer that any impact of treatment with fingolimod on the severity of relapses had not been captured in the model. In addition, the benefits from a decreased need for informal care provided by family and friends of people with multiple sclerosis had not been considered. In the manufacturer's view inclusion of these factors would decrease the ICER. The Committee accepted that fingolimod is a valuable new therapy and that its oral formulation represents innovation in the treatment of multiple sclerosis. The Committee recognised that including all of these benefits suggested by the manufacturer and patient experts in the manufacturer's model could decrease the ICER to a level that would be considered a cost-effective use of NHS resources (FAD section 4.19). The Committee debated the difficult position it had been placed in, requiring it to make a decision on the use of fingolimod compared with treatments which are not recommended by NICE but widely used within the NHS. The Committee acknowledged that the ICERs for fingolimod fell within a range which would be considered an acceptable use of NHS resources after ignoring

Consultee	Comment	Response
	would otherwise have to spend. Fingolimod is more effective at reducing relapses and disease progression compared to existing MS therapies. 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. 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. 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. 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.	that the comparators were previously deemed not cost effective by NICE. However, the Committee noted that the current risk-sharing scheme allows beta interferons to be purchased at a price which the Department of Health considers to be a cost-effective use of NHS resources; but outcome data from the scheme to justify the negotiated procurement price for these treatments are lacking. Taking these difficulties into consideration, the Committee made an exceptional case and recommended fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (population 1b). See FAD section 4.20.
Novartis Pharmaceuticals UK	**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.*	Comments noted. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3).

Consultee	Comment	Response
	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	The manufacturer's revised analysis submitted in response to the second appraisal consultation document compares fingolimod with a weighted average of beta interferons and best supportive care to reflect the current variation in clinical practice to manage RRMS. Best supportive care only represents 5% of this comparator, in line with clinical opinion.

Consultee	Comment	Response
	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%. <u>Addenbrookes hospital, Cambridge</u> Their figures for 2011 are that fewer than 3% of new DMT patients ceased treatment and went on to BSC. <u>North Midlands MS Service</u> 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." <u>Salford MS centre</u> 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. 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. 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. *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.*	

Consultee	Comment	Response
	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%.	
Novartis Pharmaceuticals UK	**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 **Error! Reference source not found.**. **Table 1 not reproduced** This results in composition of the mix of comparators as shown in Error! Reference source not found.. When this analysis is run using the updated model described in Section 0, it results in a ICER versus fingolimod of £27,820. **Table 2 not reproduced**	Comments noted. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The Committee noted that the manufacturer's probabilistic ICER for fingolimod compared with the weighted average of the comparators was £27,800 per QALY gained. The Committee acknowledged that the manufacturer had assumed that best supportive care contributes only 5% to the weighted average in the base case, and that sensitivity analyses showed that if a higher proportion was assumed, such as 10%, the ICER would increase to approximately £30,000 per QALY gained. The Committee acknowledged from the manufacturer's and the ERG's sensitivity analyses that the ICER for fingolimod compared with the weighted average of the comparators depends on the proportions assumed for the comparator treatments, and the assumptions about the natural history of disability progression and the waning of treatment effect after 5 years. The Committee concluded that the most plausible ICER for fingolimod compared with the weighted average of the comparators was likely to be in the range of £25,000 to £35,000 per QALY gained (FAD section 4.17).

Consultee	Comment	Response
	The impact of varying the proportion of BSC across the range of the reported levels of BSC (0% to 8.7%) is presented in **Error! Reference source not found.**. 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 not reproduced**	
Novartis Pharmaceuticals UK	**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* **(Not shown here)**. *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.* <u>Base case: fingolimod vs. interferon beta-1a (im) [Avonex] comparison for Population 1b</u> 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 **Error! Reference source not found.** for fingolimod versus interferon	Comments noted. The Committee noted that sensitivity analyses carried out by the manufacturer and the ERG showed that a reduction in the assumed duration of treatment effect increased the ICERs substantively. The Committee heard from the manufacturer that there is currently no evidence to support the hypothesis that the efficacy of fingolimod will reduce over time and preliminary results from the FREEDOMS extension study show that there is no loss of efficacy over 4 years. In the absence of data beyond 4 years, the Committee decided to be cautious and assume a 50% waning of treatment effect after 5 years in the base-case analysis. However, it acknowledged that if of the treatment effect did not wane over time then this would overestimate the base case ICER (FAD section 4.13). The Committee concluded that limiting the analyses to comparisons with Avonex only was not appropriate, and instead comparisons with other beta interferons and best supportive care need to be included as a basis for any recommendations in this appraisal (FAD section 4.6). The Committee considered the manufacturer's revised probabilistic base-case ICER of £17,300

Consultee	Comment	Response
	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 not reproduced** **Error! Reference source not found.** 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 not reproduced**	per QALY gained for fingolimod compared with Avonex. The Committee noted that in the ERG's incremental analysis, Avonex was extendedly dominated by fingolimod and the probabilistic ICER for fingolimod compared with best supportive care was £58,000 per QALY gained. The Committee acknowledged that the ERG's analyses demonstrated that beta-interferon treatment may not be cost effective compared with what is considered an appropriate use of NHS resources as defined in the NICE 'Guide to the methods of technology appraisal'. However it was mindful of the need to take account of current NHS practice, including the risk-sharing scheme, when defining the appropriate comparator(s) for assessment (FAD section 4.16).
Novartis Pharmaceuticals UK	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. **Error! Reference source not found.** presents the updated probabilistic ICER of £30,936 for fingolimod versus interferon beta-1a (sc). **Table 4 not reproduced** 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-	Comments noted. The Committee noted comments from the manufacturer in response to the appraisal consultation documents, which suggested that the Rebif-44 data used in the comparison with fingolimod were from patients with relapsing–remitting multiple sclerosis regardless of previous treatment, rather than from those whose disease had a suboptimal response to disease-modifying therapy (that is, population 1b). The Committee was persuaded that this may have resulted in an overestimation of the ICER for fingolimod compared with Rebif-44 (FAD section 4.15).

Consultee	Comment	Response
	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 **Error! Reference source not found.** 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. **Error! Reference source not found.** 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 not reproduced**	
Novartis Pharmaceuticals UK	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 **Error! Reference source not found.**. 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 not reproduced** 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 **(Not shown here)** for details.	Comments noted. The Committee noted that the manufacturer's probabilistic ICER for fingolimod compared with the weighted average of the comparators was £27,800 per QALY gained. The Committee acknowledged that the manufacturer had assumed that best supportive care contributes only 5% to the weighted average in the base case, and that sensitivity analyses showed that if a higher proportion was assumed, such as 10%, the ICER would increase to approximately £30,000 per QALY gained. The Committee acknowledged from the manufacturer's and the ERG's sensitivity analyses that the ICER for fingolimod compared with the weighted average of the comparators depends on the proportions assumed for the comparator treatments, and the assumptions about the natural history of disability progression and the waning of treatment effect after 5 years. The Committee concluded that the most plausible ICER for fingolimod compared with the weighted average of the comparators was likely to be in the range of £25,000 to £35,000 per QALY gained (FAD section 4.17).

Consultee	Comment	Response
	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 **Error! Reference source not found.** 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 not reproduced**	
Novartis Pharmaceuticals UK	50% waning after five years over estimates the impact of therapy waning 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. 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. The study is still being written up and only a preliminary analysis is available (**academic-in-confidence information removed**). 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	Comments noted. The Committee noted that sensitivity analyses carried out by the manufacturer and the ERG showed that a reduction in the assumed duration of treatment effect increased the ICERs substantively. The Committee heard from the manufacturer that there is currently no evidence to support the hypothesis that the efficacy of fingolimod will reduce over time and preliminary results from the FREEDOMS extension study show that there is no loss of efficacy over 4 years. In the absence of data beyond 4 years, the Committee decided to be cautious and include a 50% waning of treatment effect after 5 years in the base-case analysis. However, it acknowledged that if of the treatment effect did not wane over time then this would overestimate the base case ICER (FAD section 4.13). The Committee acknowledged from the manufacturer's and the ERG's sensitivity analyses that the ICER for fingolimod compared with the weighted average of the comparators depends on the proportions assumed for the comparator treatments, and the assumptions about the natural history of disability progression and the waning of treatment effect after 5 years. The Committee concluded that the most plausible ICER for fingolimod compared with the weighted average of the comparators was likely to be in the range of £25,000 to £35,000 per QALY gained (FAD

Consultee	Comment	Response
	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. 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 (**Error! Reference source not found.**).* **Table 8 not reproduced**	section 4.17).
Novartis Pharmaceuticals UK	**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	Comments noted. The Committee noted from subsequent sensitivity analyses carried out by the manufacturer that the ICERs increased only slightly with changes in the assumptions on natural history of disease progression. The Committee was persuaded that disease progression in people initially treated with disease-modifying treatments may be less rapid in current clinical practice than in the Ontario dataset and concluded that data on the natural history of disability progression were a source of uncertainty in the model (FAD section 4.11).

Consultee	Comment	Response
	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, 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	

Consultee	Comment	Response
	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.*	
Novartis Pharmaceuticals UK	**Summary** • 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. 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). • 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).	Comments noted. The Committee concluded that the most plausible ICER for fingolimod compared with the weighted average of the comparators was likely to be in the range of £25,000 to £35,000 per QALY gained (FAD section 4.17). The Committee made an exceptional case and recommended fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (population 1b), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See FAD sections 1.1-1.2

Consultee	Comment	Response
	• 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. • 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.*	and 4.20.
Royal College of Nursing	**Has all of the relevant evidence been taken into account?** **Answer:** Although the evidence considered seems reasonably comprehensive it is still difficult to apply this to everyday clinical practice. The RCN acknowledges appraisal of process of seeking clinical expert input and note that there were two clinical experts present. We are however, not sure that this fully covered all areas in view of the complexity and unpredictability of this condition.	Comment noted. Clinical specialists were present at the first two Committee meetings and a number of written responses from clinical professionals and their professional organisations were received during the course of the appraisal, which were considered by the Committee.
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Answer:** It appears that the actual number of patients contained within fingolimod clinical trials, that would have met the licensed criteria was very small. We consider that this could have made the ability of the Committee to determine clinical and cost effectiveness very difficult. This seems evident in the conclusion that there was no strong evidence that fingolimod was effective for that specific patient group in comparison to Avonex. In view of this, we would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by people with multiple sclerosis. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted. The Committee acknowledged that the choice of comparator in the manufacturer's model was a key driver of cost effectiveness. It also acknowledged that there was variation in current practice and therefore concluded that fingolimod should be compared with a weighted average of the comparators currently used in UK clinical practice to manage relapsing–remitting multiple sclerosis. This includes best supportive care together with a mix of beta interferons (with the proportions for the beta interferons based on market share data from the Prescription Pricing Authority). See FAD section 4.17.
Royal College of Nursing	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**	Comment noted. The final draft guidance recommends the use of fingolimod as an option

Consultee	Comment	Response
	Answer: The RCN is disappointed that the Appraisal Committee does not recommend the use of Fingolimod for the treatment of relapse remitting multiple sclerosis. Fingolimod is the first oral medication that has been well tolerated. The clinical management of Multiple Sclerosis is far more complex and unpredictable than demonstrated by the model used and evidence presented. It is stated that the Committee has taken into consideration the specialist and patient comments, but has gone on to decline its use. We acknowledge the decision. The document clearly describes the reasoning for the decision. We agree that choice of comparator is crucial, but consider that the selection of Avonex was inappropriate given the marketing authorisation for fingolimod and that the Committee was obliged to limit consideration within the submission. It is frustrating that additional disease modifying treatment is not yet available. Had standard best practice (ie no treatment) been selected there may have been an ethical argument to suggest that the small number of patients who would fail treatment with other Disease Modifying Treatments (DMTs) should be offered fingolimod.	for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
Royal College of Nursing	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** **Answer:** None that we are aware of.	Comment noted.
Royal College of Nursing	**Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?** **Answer:** We are not aware of any specific issue at this stage. However, it would be helpful to know if NICE will publish the equality analysis for this appraisal. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comment noted. An equality impact assessment is published on the NICE website alongside all appraisals.
Association of British Neurologists	We are grateful for the NICE Committee's further consideration of fingolimod for the group of people with sub-optimally controlled relapsing-remitting multiple sclerosis. We note the incorporation of the new 'patient-access scheme' and also the continued concerns expressed by the NICE committee. You will already be in receipt of our previous submission following the first	Comments noted. The manufacturer's response to the second appraisal consultation document highlights that 1/3 of treatment-naïve patients with RRMS may receive best supportive care, however this is a different population to that considered in this appraisal, (that is, those who have had a

Consultee	Comment	Response
	appraisal document and we stand by our initial comments made at that time. We would further like to express our disappointment at the continued incorporation of point 4.18 in the most recent appraisal document and ask you to re-consider: 'The Committee heard from the ERG that its clinical advisers had estimated that approximately one-third of people with relapsing–remitting multiple sclerosis whose disease has a suboptimal response to beta-interferon treatment will receive best supportive care in the UK'. We feel this assumption is incorrect and does not reflect typical practice within the UK. Standard practice would be switching to an alternative beta-interferon, glatiramer acetate or consideration depending on whether criteria were met: natalizumab, alemtuzumab or mitoxantrone. Although there are no agreed figures regarding this particular issue it is our view that the figure of one-third receiving best supportive care alone is a significant overestimate. We are concerned that in using this figure there is potential for inaccuarcy in the model used. We note that the incorporation of one third as a value regarding this issue is not based on published evidence but on comments your committee received.	suboptimal response to previous therapy).The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The manufacturer's revised analysis submitted in response to the second appraisal consultation document compares fingolimod with a weighted average of beta interferons and best supportive care to reflect the current variation in clinical practice to manage RRMS. Best supportive care only represents 5% of this comparator, in line with clinical opinion.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Clinical Expert	**<u>Use of only Avonex (a form of beta interferon) as comparator treatment</u>** I agree with the concerns of the Committee that this was not the best comparator, given that the subgroup 1b had been defined by inadequate treatment response on beta interferon ("highly active disease that has remained unchanged or worsened despite treatment with beta interferon"). However, I disagree that "best supportive care" should be the choice of comparator as patients with inadequate response to beta interferon may be switched to another disease modifying treatment *in addition* to best supportive care.	Comment noted. The Committee acknowledged that based on current practice in the NHS it would be inappropriate to use Avonex alone as a comparator for fingolimod (FAD section 4.15). The Committee acknowledged that the choice of comparator in the manufacturer's model was a key driver of cost effectiveness. It also acknowledged that there was variation in current practice and therefore concluded that fingolimod should be compared with a weighted average of the comparators currently used in UK clinical practice to manage relapsing–remitting multiple sclerosis. This includes best supportive care together with a mix of beta interferons (with the

Nominating organisation	Comment	Response
		proportions for the beta interferons based on market share data from the Prescription Pricing Authority). See FAD section 4.17.
Clinical Expert	**Option of best supportive care** I am not aware of any evidence base for the assertion that the "ERG … clinical advisers had estimated that approximately one-third of people with relapsing–remitting multiple sclerosis whose disease has a suboptimal response to beta-interferon treatment will receive best supportive care in the UK (4.18)." My information and experience about management of people with RRMS whose disease has had a suboptimal response to beta-interferon does not include best supportive care. Instead such patients may remain on their existing DMT, or be switched to another first line agent, or be changed to natalizumab, or sometimes mitoxantrone or alemtuzumab; details as laid out in my written submission to NICE (May 2011) or my previous comments (August 2011) or in my verbal evidence as summarised in paragraph 4.3 and reproduced below. *The Committee heard from the clinical specialists that after a suboptimal response to the first disease-modifying treatment used, clinicians are likely to either offer a different beta interferon or glatiramer acetate, or offer the patient a higher dose of beta interferon (such as Rebif-44). The Committee also heard that clinicians are generally reluctant to stop treatment altogether after a suboptimal response.*	Comments noted. The manufacturer's response to the second appraisal consultation document highlights that 1/3 of treatment-naïve patients with RRMS may receive best supportive care, however this is a different population to that considered in this appraisal, (that is, those who have had a suboptimal response to previous therapy).The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The manufacturer's revised analysis submitted in response to the second appraisal consultation document compares fingolimod with a weighted average of beta interferons and best supportive care to reflect the current variation in clinical practice to manage RRMS. Best supportive care only represents 5% of this comparator, in line with clinical opinion.
Clinical Expert	*"approximately one-third of people with relapsing–remitting multiple sclerosis whose disease has a suboptimal response to beta-interferon treatment will receive best supportive care in the UK. The Committee heard from the clinical specialists at the meeting that this estimate was likely to be correct."* The clinical specialists are unspecified but I do not recollect concurring with this assertion, please see above for my written and verbal evidence on management for people with a suboptimal response to beta-interferon treatment. I would also not anticipate that a MS specialist nurse would agree with this estimate on use of best supportive care in place of disease modifying therapy.	Comment noted. The manufacturer's response to the second appraisal consultation document highlights that 1/3 of treatment-naïve patients with RRMS may receive best supportive care, however this is a different population to that considered in this appraisal, (that is, those who have had a suboptimal response to previous therapy). The Committee heard from the clinical specialists that after a suboptimal response to the first

Nominating organisation	Comment	Response
		disease-modifying treatment used, clinicians are likely either to offer a different beta interferon or glatiramer acetate, or offer the patient a higher dose of beta interferon (such as Rebif-44). The Committee also heard that clinicians are generally reluctant to stop treatment altogether after a suboptimal response (FAD section 4.3).
MS Specialist Nurse	**3.8 (page 10 of 48)** The model is based on a Markov cohort approach and estimates disease progression through 21 disability states that are defined by EDSS score (ranging from 0 to 10) and account for disability for patients with relapsing–remitting multiple sclerosis (10 states), patients with secondary progressive multiple sclerosis (10 states) and death. **In each cycle of the model, a patient with relapsing–remitting multiple sclerosis can progress to a worse EDSS state or remain in the same state.** **Comment** – patients with RRMS can experience a significantly worsening EDSS score during relapse and can return a much improved EDSS over time. This time span is not predictable.	Comment noted. The Committee noted the concerns of the clinical specialists that the manufacturer's model may not reflect the natural history of multiple sclerosis because it does not allow for improvement in EDSS scores. The Committee heard from the manufacturer that the ability to include improvements in EDSS scores had been intentionally removed from the model to produce a conservative estimate of the cost effectiveness of fingolimod. The Committee heard from the clinical specialists that few people experience an improvement in EDSS score and therefore it concluded that the manufacturer's approach was reasonable (FAD section 4.10).
MS Specialist Nurse	**3.8 (page 10 of 48)** **People with an EDSS score greater than 6, or with secondary progressive multiple sclerosis, are assumed to receive best supportive care.** **Comment -** people with an EDSS greater than 6 cannot be assumed to only receive best supportive care as it may be a transitory score.	Comment noted. Please see previous response.
MS Specialist Nurse	**3.20 (page 15 of 48)** The ERG also noted that the results from the manufacturer's mixed treatment comparisons did not yield clear differences between the beta interferons in patients with relapsing– remitting multiple sclerosis in terms of disease progression and annualised relapse rates. It cautioned that a comparison solely with Avonex could underestimate the ICER of fingolimod and **therefore reasoned that a comparison with best supportive care would have been more appropriate.** **Comment** – a comparison with Tysabri would be more appropriate and BSC only appropriate at end stage MS when all other treatment options are inappropriate.	Comment noted. Tysabri (natalizumab) is only recommended for the treatment of rapidly evolving severe relapsing remitting multiple sclerosis (please refer to NICE technology appraisal 127). The Committee heard from the clinical specialists that fingolimod would provide the greatest benefit to people with rapidly evolving severe relapsing–remitting multiple sclerosis, because they currently have very few treatment options. The Committee acknowledged the clinical specialists'

Nominating organisation	Comment	Response
		disappointment that a specific recommendation for the use of fingolimod in this population could not be made because the manufacturer had not submitted an analysis of fingolimod compared with natalizumab in this population (FAD section 4.4). The Committee acknowledged that the choice of comparator in the manufacturer's model was a key driver of cost effectiveness. It also acknowledged that there was variation in current practice and therefore concluded that fingolimod should be compared with a weighted average of the comparators currently used in UK clinical practice to manage relapsing–remitting multiple sclerosis. This includes best supportive care together with a mix of beta interferons (with the proportions for the beta interferons based on market share data from the Prescription Pricing Authority). See FAD section 4.17.
MS Specialist Nurse	**4.3 (page 24 of 48)** The Committee heard from the clinical specialists that after a suboptimal response to the first disease-modifying treatment used, clinicians are likely to either offer a different beta interferon or glatiramer acetate, or offer the patient a higher dose of beta interferon (such as Rebif-44). **The Committee also heard that clinicians are generally reluctant to stop treatment altogether after a suboptimal response.** **Comment** – this clinical decision is made as suboptimal response does not necessarily represent treatment failure and discontinuation of treatment could initiate potential deterioration in disease. In this case scenario BSC would still not represent the most effective care choice.	Comment noted. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The manufacturer's revised analysis submitted in response to the second appraisal consultation document compares fingolimod with a weighted average of beta interferons and best supportive care to reflect the current variation in clinical practice to manage RRMS. Best supportive care only represents 5% of this comparator, in line with clinical opinion.

Nominating organisation	Comment	Response
MS Specialist Nurse	**4.18 (page 33 of 48)** The Committee heard from the **ERG that its clinical advisers had estimated that approximately one-third of people with relapsing–remitting multiple sclerosis whose disease has a suboptimal response to beta-interferon treatment will receive best supportive care in the UK. The Committee heard from the clinical specialists at the meeting that this estimate was likely to be correct.** **Comment -** The notes do not identify the clinical specialists but I do not remember agreeing with this estimate and I have added additional comment below. My Neurologist colleagues would not concur with this estimate on use of best supportive care in place of disease modifying therapy either.	Comment noted. The manufacturer's response to the second appraisal consultation document highlights that 1/3 of treatment-naïve patients with RRMS may receive best supportive care, however this is a different population to that considered in this appraisal, (that is, those who have had a suboptimal response to previous therapy).The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3).
MS Specialist Nurse	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). The Committee estimated that the ICER for fingolimod compared with a comparator made up of equal proportions of best supportive care, Avonex and Rebif-44 using the manufacturer's revised model, would be approximately £40,000 per QALY gained (patient access scheme included). The Committee concluded this to be a starting point for its decision, and noted that using a probabilistic analysis (see section 4.9) and the following, more plausible assumptions, would increase this ICER…. **Comment -** this is a misunderstanding of the supposition made by the clinical experts that roughly a third of patients who might be considered eligible for disease modifying treatment will defer that treatment option and take a "watchful wait" position (this could be possibly considered BSC). It is highly unlikely that as much as a third of the suboptimal response group will actively receive *only* BSC as treatment of choice. Discontinuation of treatment is a rare decision as it risks an unknown outcome in terms of disease activity. This is a choice likely to be made only when someone is in the end stage of their MS.	Comment noted. The manufacturer's response to the second appraisal consultation document highlights that 1/3 of treatment-naïve patients with RRMS may receive best supportive care, however this is a different population to that considered in this appraisal, (that is, those who have had a suboptimal response to previous therapy).The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3).

Comments received from commentators

Commentator	Comment	Response
Evidence Review Group	**ACD2, suggestions and comments**	Comments noted. The FAD has been updated to

Commentator	Comment	Response
	3.11 The sentence "The probabilities of annual relapse rate and disability progression for fingolimod treatment were calculated from the absolute incidences of these outcomes in the FREEDOMS trial." is incorrect. Only relative effectiveness measures were derived from the FREEDOMS trial. **3.12** The following statement is incorrect and unclear "an adjustment was made to reflect the time since diagnosis and to account for relapses". This should state "an adjustment was made to account for relapses". **3.20** The statement "therefore reasoned that a comparison **with** best supportive care would have been more appropriate.", for accuracy, should be changed to "therefore reasoned that a comparison **including** best supportive care would have been more appropriate.". The ERG advocates for an incremental analysis where all relevant comparators are included, and not a sole comparison against best supportive care. **3.21** For clarity, reference back to section 3.16. **3.24** The statement "In addition, Avonex was extendedly dominated by fingolimod and best supportive care (that is, Avonex was more expensive and less effective than either fingolimod or best supportive care)" is incorrect. It should read "In addition, Avonex was extendedly dominated by fingolimod (the ICER of Avonex is higher than that of fingolimod in an incremental analysis, meaning that a unit of health benefit is attained at a higher cost than with fingolimod)". The notion of extended dominance has been misinterpreted throughout this document – this needs to be corrected. For accuracy the statement "The ERG considered that this analysis provided further evidence that best supportive care rather than Avonex should have been considered as the primary comparator to fingolimod for population 1b." should be re-worded to "The incremental analyses show that, in both populations, Avonex is either dominated or extendedly dominated by fingolimod. The ERG considered that the cost effectiveness of fingolimod should be expressed in the context of this incremental analysis." **3.25** The statement "the ERG had previously explored a number of alternative scenarios for incorporating trial utility data into the model, which were shown to increase the ICERs" is incorrect. The ERG explored a number of scenarios showing that the ICER changes, sometimes increasing sometimes decreasing; the manufacturer selected one scenario that showed the greatest decrease in	incorporate your suggested changes where appropriate.

Commentator	Comment	Response
	the ICER without providing justification for this choice. **3.27** The statement "However, for population 1b, Rebif-44 was dominated by best supportive care and extendedly dominated by fingolimod (that is, Rebif-44 was more expensive and less effective than either best supportive care or fingolimod)" is inaccurate. It should be changed to "However, for population 1b, Rebif-44 was extendedly dominated by fingolimod (that is, Rebif-44 was less expensive and less effective than fingolimod, but presents a higher incremental ICER than fingolimod)". **3.28** The statement "To explore this, the ERG re-ran the original model and excluded all **adjustments to** direct treatment effects on relapse rates." Should be changed to "To explore this, the ERG re-ran the original model and excluded all direct treatment effects on relapse rates." **3.31** The statement "The ERG cautioned that despite the discounted drug acquisition cost, the remaining uncertainty in the model still remained." Should be changed to "The ERG cautioned that despite the discounted drug acquisition cost, the remaining uncertainties around the model **and inputs used to inform the model** were still unresolved and unaccounted for."	

Summary of comments received from members of the public

Theme	Response
Disagreement with assumption that 1/3 of patients whose disease has not responded to beta interferon then receive best supportive care. In clinical practice, patients would remain on existing treatment, switch to an alternate betainterferon or glatiramer acetate or natalizumab, or have their dose increased for their existing treatment or switch to an unlicenced alternative (e.g. alemtuzumab). Best supportive care is not an appropriate comparator.	Comment noted. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3). The Committee acknowledged that the choice of comparator in the manufacturer's model was a key driver of cost effectiveness. It also acknowledged that there was variation in current practice and therefore concluded that fingolimod should be compared with a weighted average of the comparators currently used in UK clinical practice to manage relapsing–remitting multiple sclerosis. This includes best supportive care together with a mix of beta interferons (with the proportions for the beta interferons based on market share data from the Prescription Pricing Authority). See FAD

Theme	Response
	section 4.17.
Multiple sclerosis discriminates against young women. Denying fingolimod to patients will impact largely on their children and family. It is unethical not to recommend fingolimod.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
Patients frequently switch between treatments in an attempt to optimise both efficacy and tolerability. Best supportive care would only be used in 5-10% of patients.	Comment noted. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3).
It is disappointing that the provisional recommendation is not positive.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
Fingolimod is an oral tablet which is more convenient and socially acceptable than injectable or IV treatments. It also offers a suitable treatment option to patients with needle-phobia.	Comment noted. The Committee accepted that fingolimod is a valuable new therapy and that its oral formulation represents innovation in the treatment of multiple sclerosis (FAD section 4.19).
Patients are often anxious about the health risks associated with natalizumab treatment and would prefer to take fingolimod instead.	Comment noted. The Committee heard from the clinical specialists that fingolimod would provide the greatest benefit to people with rapidly evolving severe relapsing–remitting multiple sclerosis, because they currently have very few treatment options. The Committee acknowledged the clinical specialists' disappointment that a specific recommendation for the use of fingolimod in this population could not be made because the manufacturer had not submitted an analysis of fingolimod compared with natalizumab in this population (FAD section 4.4).
The provisional recommendations fail to take into consideration the subgroup of patients that are unable to receive (or continue) natalizumab, that is those with	Comment noted. The Committee heard from the clinical specialists that fingolimod would provide the greatest benefit to people with rapidly evolving severe relapsing–remitting multiple sclerosis, because they currently have

Theme	Response
rapidly-evolving severe (RES) RRMS.	very few treatment options. The Committee acknowledged the clinical specialists' disappointment that a specific recommendation for the use of fingolimod in this population could not be made because the manufacturer had not submitted an analysis of fingolimod compared with natalizumab in this population (FAD section 4.4).
The stress of being denied a treatment with proven efficacy (fingolimod) has a profound effect on a patient's quality of life.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case). See sections 1.1-1.2 and 4.20 of the FAD for more information.
Fingolimod improves a patient's ability to perform daily activities and has a large impact on their quality of life. It may also enable patients to return to work and enable them to contribute to society.	Comment noted. The Committee discussed whether the assessment of the change in health-related quality of life had been inadequately captured in the economic analysis. It heard from the patient experts that treatment with fingolimod significantly reduces relapses and could allow people to lead an active and fulfilling life and contribute more fully to society (FAD section 4.19).
The Committee has placed too much emphasis on the cost of fingolimod rather than on patient care and well-being.	Comment noted. When making its decision, the Committee has considered all of the clinical and economic evidence provided by the manufacturer and the Evidence Review Group as well as the submissions and statements from patient groups, professional organisations, clinical specialists and the general public. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
Fingolimod should be made available on the NHS to everyone who needs it. It is short-sighted to cut costs in this area.	The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part

Theme	Response
	of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
Proposed review date of January 2015 is too long.	The guidance will only be reviewed when new evidence becomes available which is likely to impact on the current recommendations.
Patients should be allowed to take fingolimod until further research is undertaken.	The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case) and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information. People currently receiving fingolimod whose disease does not fulfil these criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop (FAD section 1.2).
If not approved by NICE, people will be denied an effective treatment that is available in other countries.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
Treatment with fingolimod would help patients remain relapse-free for longer periods of time which means that they will require less assistance from the NHS during this time	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
The decision doesn't take into account the adverse effects of injectable treatments which necessitate additional treatment (such as antibiotics, dressings, hospitalisation) which incur large costs to the NHS.	Comment noted. The Committee discussed whether the assessment of the change in health-related quality of life had been inadequately captured in the economic analysis. It heard from the patient experts that people who receive fingolimod have fewer adverse reactions than those who receive beta-interferon therapy. The Committee recognised that including all of the

Theme	Response
	benefits suggested by the manufacturer and patient experts in the manufacturer's model could decrease the ICER to a level that would be considered a cost-effective use of NHS resources (FAD section 4.19).
A negative recommendation from NICE will make the use of fingolimod a postcode lottery which is inherently unfair and unethical.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
For patients for whom natalizumab is not appropriate, there are no other treatment options currently available on the NHS.	Comment noted. The Committee heard from the clinical specialists that fingolimod would provide the greatest benefit to people with rapidly evolving severe relapsing–remitting multiple sclerosis, because they currently have very few treatment options. The Committee acknowledged the clinical specialists' disappointment that a specific recommendation for the use of fingolimod in this population could not be made because the manufacturer had not submitted an analysis of fingolimod compared with natalizumab in this population (FAD section 4.4).
It would be unethical to stop treatment for patients currently responding well to fingolimod (for example, those who are in clinical trials).	The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information. People currently receiving fingolimod whose disease does not fulfil these criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop (FAD section 1.2).
The manufacturer should be encouraged to continue research for fingolimod, expand on the potential patient population and reconsider the costs of the patient access scheme.	Comment noted. The Committee recommends the development of patient registries for multiple sclerosis to capture long-term treatment-related outcomes (FAD section 6.1). The Committee recommends that a new model for multiple sclerosis be developed, ideally based on UK patient cohorts, which uses the best available evidence (including experience to date from the risk-sharing

Theme	Response
	scheme) and includes all currently available treatments (FAD section 6.2).
EDSS scores constantly fluctuate; too much emphasis has been placed on them in this appraisal.	Comment noted. The Committee noted the concerns of the clinical specialists that the manufacturer's model may not reflect the natural history of multiple sclerosis because it does not allow for improvement in EDSS scores. The Committee heard from the manufacturer that the ability to include improvements in EDSS scores had been intentionally removed from the model to produce a conservative estimate of the cost effectiveness of fingolimod. The Committee heard from the clinical specialists that few people experience an improvement in EDSS score and therefore it concluded that the manufacturer's approach was reasonable (FAD section 4.10).
There is an unmet need for fingolimod, especially for patients who cannot tolerate injectable treatments due to significant lipoatrophy or injection site reactions; those who are allergic or sensitive to natalizumab or who are experiencing breakthrough relapses but choose not to receive natalizumab because of the risk of PML.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information. The Committee heard from the clinical specialists that fingolimod would provide the greatest benefit to people with rapidly evolving severe relapsing–remitting multiple sclerosis, because they currently have very few treatment options. The Committee acknowledged the clinical specialists' disappointment that a specific recommendation for the use of fingolimod in this population could not be made because the manufacturer had not submitted an analysis of fingolimod compared with natalizumab in this population (FAD section 4.4).
Fingolimod could mean the difference between many people staying fit enough to work and lead their lives independently instead of having no future and having to live a life dependent on the state and others.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
The FREEDOMS trial showed significant improvement in disability and MRI	Comment noted. The final draft guidance recommends the use of

Theme	Response
endpoints. The negative recommendation from NICE is purely a cost driven statement.	fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
Fingolimod's impact on quality life has been inadequately considered. 'The improvement in quality of life after taking fingolimod is huge'.	Comment noted. The Committee discussed whether the assessment of the change in health-related quality of life had been inadequately captured in the economic analysis. It heard from the patient experts that treatment with fingolimod significantly reduces relapses and could allow people to lead an active and fulfilling life and contribute more fully to society (FAD section 4.19).
Multiple sclerosis is not a disease that lends itself to statistical modelling: relapses create too many u-shaped data to account for. A far simpler assessment approach is warranted.	Comment noted. The Committee emphasised that it is important that a new model for multiple sclerosis is developed for any future appraisals of treatments for multiple sclerosis. The new model should ideally be based on UK patient cohorts, should use the best available evidence (including experience to date from the risk-sharing scheme) and should include all currently available treatments, so that future appraisals of treatments for multiple sclerosis are directly relevant to UK clinical practice (FAD section 4.20).
Fingolimod is already approved for use in many European countries, USA, Japan and Australia. The UK is lagging behind.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
The Committee has undervalued the advance that fingolimod represents.	Comment noted. The Committee accepted that fingolimod is a valuable new therapy and that its oral formulation represents innovation in the treatment of multiple sclerosis (FAD section 4.19).
Comparator treatments should also have their delivery costs taken into account. Supplies of hypodermic needles and needle disposal resources are a vast cost.	Comment noted. These costs were not included in the manufacturer's model.
Evidence shows that immunomodulatory therapies are most effective during an	Comment noted. The final draft guidance recommends the use of

Theme	Response
early therapeutic window of disease, ideally the first 5 years. Early in the disease trajectory, there is evidence that immunomodulatory therapies can delay permanent disability accumulation including for fingolimod.	fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.
Early and optimal control of inflammatory disease is important to the long-term outcomes of patients with RRMS. One-third of patients have a sub-optimal response to first-line DMTs. Discontinuing DMT in patients with aggressive disease puts them at increased risk of early disability and death. Non-responders should be switched to another first-line therapy. Best supportive care is only appropriate in relatively rare circumstances where an appropriate alternative DMT cannot be found.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information. The Committee heard from the clinical specialists that after a suboptimal response to the first disease-modifying treatment used, clinicians are likely either to offer a different beta interferon or glatiramer acetate, or offer the patient a higher dose of beta interferon (such as Rebif-44). The Committee also heard that clinicians are generally reluctant to stop treatment altogether after a suboptimal response. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments (FAD section 4.3).
The proposed patient group for whom NHS funding is sought reflects clinical opinion on the group of patients who, based on clinical activity, would benefit from a change in therapy.	Comment noted. The final draft guidance recommends the use of fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite previous treatment with beta interferon (that is, population 1b from the manufacturer's base case), and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. See sections 1.1-1.2 and 4.20 of the FAD for more information.