Comments to ICER's Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value Draft Evidence Report

We acknowledge the difficult nature of comparing the effectiveness of the DMTs approved for the treatment of RRMS, given the limited number of head-to-head trials and lack of real-world data. We agree with the many limitations of this review, all of which add to uncertainty when comparing across trials:

- The MS trial population is somewhat different over time, as MS diagnostic criteria have evolved significantly since the early MS trials.
- The definition of relapses is not consistent across trials.
- EDSS was used to measure disability in most of the DMT clinical trials; EDSS is frequently criticized for being insensitive to small changes, being heavily dependent on mobility, being subjective in some assessments with high intra- and inter-rater variability, & not capturing the full range of patient disabilities.
- The definition of sustained disability progression is not consistent across trials; some trials measured sustained disability progression over 12 weeks and some measured over 24 weeks. Because some patients have resolution of symptoms between 12 and 24 weeks of follow-up; sustained disability progression observed at 24 weeks is generally lower than at 12 weeks. A critical step to conducting a quality network meta-analysis is to ensure you are comparing the same endpoint. These endpoints are not the same.
- MRI technology has evolved significantly since the early MS trials, leading to challenges in comparing MRI outcomes across studies.

Because of the limitations when comparing across trials and until more real world data is available, treatment choice for initial therapy as well as subsequent therapies following treatment failure should continue to be a shared decision between the patient and the treating physician, and payers should make every effort to keep a variety of therapeutic options available for their patients.

Page 2 – Scope of the Assessment: We recommend expanding the scope of the assessment to include the use of the DMT prescribing information when necessary to provide more comprehensive data on safety & efficacy.

Page 2, 4, and 14 – Analytic Framework, Figure 1: There seems to be a disconnect between the Analytic Framework and the actual ICER Cost Effectiveness/Budget Impact analysis performed. The analytical framework includes health care utilization outcomes as well as many clinical & patient-centered outcomes measures that are important for employers and patients– permanent disability, days at work, cognitive function, quality of life, etc. These costs do not appear to be included in the cost effectiveness model.

The data used for ICER's analysis had an age of MS onset of 29 years (Page 60), a population for which employers (the ultimate payer for 160MM lives) would use a 10-15 year time horizon to evaluate. We encourage ICER to take a look at cost effectiveness over a longer time horizon (minimum of 10-15 years). If the MS patient becomes permanently disabled, the model should also include lost lifetime wages and the lost taxes tied to those wages, as well as the disability payments and other costs that those patients would incur.

Page 2 – Interventions: The review should be limited to products FDA-approved for the treatment of RRMS and PPMS; Rituximab should not be included in the review and ocrelizumab should only be included if it is FDA-approved prior to the final report publication. Additionally, there was not enough evidence to assess disability progression, net health benefit, or cost effectiveness of rituximab, further supporting our position that it should not be included in the report.

Page 6 – Timing: The report evaluated evidence on harms from studies of at least three months' duration. Most of the MS DMT clinical trials were relatively short duration and some new adverse events were identified through post-marketing surveillance, so the SAE rates from the prescribing information should be used, rather than clinical trial data alone, for a more accurate picture of the safety profiles of the DMTs and to better estimate costs associated with SAEs.

Page 7 - The Topic in Context: There should be more discussion about the reasons payers should offer more treatment choice and about the need for treatment switch. In addition to the patient preferences mentioned and important factors for shared decision-making about choice of DMT, please consider adding the following:

- Patients with MS present differently; you never know when a relapse will be a minor inconvenience or will result in substantial irreversible disability and significant cost; preventing relapses is critical.
- Individual patient responses to DMTs and response to DMTs as the disease progresses are also components of treatment decisions.

- As the disease progresses, patients may experience suboptimal response to their current therapy, necessitating a treatment switch. This is common in patients who develop neutralizing antibodies to beta interferons.
- The Multiple Sclerosis Coalition suggests a therapy with a different MOA be considered in the event of signs or symptoms of suboptimal response, including continued clinical and/or MRI disease activity while on treatment.

Page 8: In Paragraph 2, please change "progressive multifocal encephalopathy" to "progressive multifocal leukoencephalopathy."

Page 9 – Table 1: The following corrections should be made to the daclizumab row:
- Zinbryta is now registered; please replace the "TM" with "®".
- Zinbryta's Class is an IL-2 Modulator (anti-CD25 monoclonal antibody)
- Zinbryta's FDA-approved dose is 150 mg once a month; not every 4 weeks.

Page 9 – Table 1: There appears to be a calculation error for Year 1 WAC, based on the Redbook unit price extrapolated to 365 days for the following DMTs: *PriceRx, Medispan, and Redbook*
- Interferon B-1a (Avonex): $78,710 (not $75,881) – Calculation: WAC x (365/28)
- Interferon B-1b (Betaseron): $81,065 (not $69,220) - Calculation: 6218.71 x (365/28)
- Interferon B-1b (Extavia): $67,625 (not $57,743) - Calculation: 5558.21 x (365/30)
- Interferon B-1a (Rebif): $81,911 (not $77,827) – Calculation: 6283.57 x (365/28)
- Peginterferon B-1a (Plegridy): $75,881 (not $73,017) – Calculation: 5821.00 x (365/28)

Page 9 – Table 1: The FDA-approved dose for alemtuzumab is as follows: 12 mg/day x 5 consecutive days followed by 12 mg/day x 3 consecutive days 12 months later.

Page 10 – Table 1: If ICER decides to keep rituximab in the report, under "FDA Approved Dose" there should be a note stating that rituximab is not FDA-approved for MS; otherwise the information is misleading.

Page 13- Measures Using MRI: MRI technology has evolved significantly since the early MS trials, leading to challenges in comparing results across studies. Please add "According to the MS Coalition, evidence of new MRI activity suggests suboptimal response to DMT, & a change in DMT therapy/MOA should be considered."

Page 14 – Paragraph 1 states the economic hardships that are underappreciated in most economic analyses of MS. It does not appear that these costs were built into this model either, making the model not true to real life.

Page 14 - Paragraph 2 states that "For instance, Medicare patients pay an average of more than $6,000 in out-of-pocket costs per year for Avonex, Tecfidera, or Copaxone." It should be mentioned that year-to-date in 2016, 63% of MS claims were Commercial and 26% were Medicare and Commercial patients have significantly lower out-of-pocket costs than Medicare patients. Additionally, the majority of Medicare patients taking DMTs are eligible for extra help, so their out-of-pocket cost is minimal.

Page 14 - Paragraph 3 mentions that patients would like more data regarding the effect of DMTs on patient-reported outcomes. While patient-reported outcomes are not primary endpoints in clinical trials, they are often measured. When available, detailed clinical trial data on patient-reported outcomes should be included in the report, even if they can't be compared across DMTs.

Page 16 – Paragraph 3 mentions that all payers made use of step therapy to manage therapies for MS, typically a contraindication, intolerance, or inadequate response to one or more preferred injectable therapies (not including daclizumab) or an oral agent. This is not consistent with the model assumption of all DMTs as first-line agents.

Pages 17-19 - Table 4 – Please update the daclizumab information as follows:
- Humana: Daclizumab is Tier 5, ST Yes, PA Yes, Preferred Agent No
- Health Net: Take N/A out of preferred agent for DAC (it is not there for any other agent)
- BSCA: DAC is SP tier, ST Yes, PA Yes

Page 20: Canadian Agency for Drugs and Technology in Health & Page 21: NICE: While this information provides a perspective of how MS is treated in other countries, the AAN draft guidelines and the MS Coalition consensus guidelines are the only guidelines established by U.S. physicians.

Page 21 – MS Coalition, 2016: Please add "The MS Coalition also suggests considering alternative regimens, such as a different MOA, in the event of suboptimal response suggested by additional clinical and/or MRI disease activity."

Pages 26-28: Quality of Individual Studies (Daclizumab) and Pages 117-119: Table C3. Quality Assessment of Included RCTs of DMTs for RRMS: SELECT and DECIDE should meet Good criteria.

On Page 27, it states "We judged the study to be of fair quality, primarily because disability progression sustained for 24 weeks was not reported as well as the short follow-up (one year) and relatively large loss to follow-up (11%) for a one-year study. Please consider the following information: While 24-week confirmed disability progression (CDP)

was not a pre-specified endpoint in the SELECT trial (FDA requirement to include 12-week CDP), a post-hoc analysis presented at ECTRIMS 2012 showed a 56% relative risk reduction for daclizumab (pooled doses) vs. PBO in 24-week CDP (95% CI: 16–77) *P*=0.012. *Havrdova E, et al. ECTRIMS 2012, P949.* The majority of MS clinical trials are one year or less. The stated 11% loss to follow-up for SELECT is not consistent with the publication cited or the table on Page 119; both indicate 9% loss to follow-up. Additionally, the USPSFT criteria for a Good study states it meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent) (Loss to follow up no greater than 20%) Based on this evidence, SELECT appears to meet all of the criteria of a Good study.

On Page 119, for SELECT, the table states "No" under Key Outcomes Assessed column and "Fair" under the Quality column. Please update the columns to "Yes" and "Good", respectively.

On Pages 27-28 it states that the DECIDE trial was judged to be of Poor quality primarily because of the large loss to follow-up [23%, >20% at 144 weeks]. DECIDE was one of the largest and longest studies in MS. The DECIDE trial allowed treatment up to 144 weeks or until the last patient reached 96 weeks. The mean length of treatment in the trial is beyond 96 weeks; comparing it to standards which may have been developed for trials for 1-2 years duration may not be appropriate. The loss to follow-up rate in the DECIDE trial at 48 weeks was 12% for Avonex and 7% for Zinbryta and at 96 weeks (a duration longer than most of the other DMTs' follow-up), 20% for Avonex and 16% for Zinbryta (18% blended). Both of these fit within the USPSFT criteria for a Good study. There is no mention on page 28 of why the table states "No" for "Key Outcomes Assessed." All key outcomes were included in the DECIDE trial. The 24-week CDP was reported in the Kappos 2015 Supplement, Table 3, and should be added to page 28 as follows: Compared to IFNβ-1a at Week 144, Zinbryta was associated with a 27% relative risk reduction of 24-week confirmed disability progression (HR = 0.73) [95% CI: 0.55, 0.98] p=0.0332). On Page 119 for DECIDE, the table states "No-23%" in the Maintain Comparability column. Please replace this with Yes – 18% to reflect the 96 week rate. Additionally, please change the "No" to "Yes" for Key Outcomes Assessed, as indicated above. Please change "Poor" to "Good" under the Quality column. The DECIDE trial was a double-blind, double-dummy clinical trial; this stands in contrast to the rater-blinded design utilized for several other agents, including Rebif and Lemtrada. Was a sensitivity analyses conducted to evaluate the impact of the trial design?

Page 127, Table C5: Please consider including the SELECT 24-week CDP reported by *Havrdova E, et al. ECTRIMS 2012, P949.* Additionally, please update the table with the DECIDE 24-week CDP data according to the Kappos supplement, Table S3 [18% Avonex, 13% Zinbryta; HR=0.73 (0.55 to 0.98) *P*=0.03]. Please consider including this information in the Base Case NMA, as it is not appropriate to compare across different end points in a NMA.

Page 27: The statement that the HR for CDP sustained for at least 12 weeks was 0.45 is not consistent with the table on page 131, which states the HR is 0.43. Both should state 0.43.

Page 27: The report states "There were also significant improvements in quality of life as measured by the Multiple Sclerosis Impact Scale (MSIS-29) physical score, the EuroQol five dimensions (EQ-5D) summary health index, and the 12-item short form health survey (SF-12) physical and mental health components for daclizumab compared to placebo." However, MSIS-29 PHYS was not statistically significant within the sequential closed testing procedure. We suggest adding EQ-VAS, as it is mentioned elsewhere in the report.

Page 28, Paragraph 1, Line 5 states ARR for daclizumab was lower for daclizumab compared to placebo. Please replace "placebo" with "interferon beta-1a 30 mcg IM".

Page 28: The report states "The DECIDE trial randomized 1,841 patients to daclizumab or interferon β-1a 30 mcg IM each week for up to 144 weeks (median 108.7 weeks)." However, 108.7 weeks was the median duration in daclizumab group only. Median duration for IFN was 111.4 wks.

Additionally, we suggest adding "150 mg sc" to clarify the daclizumab dose in the DECIDE trial.

Page 28: The report states "The primary outcome compared the relapse rate for each arm using negative binomial regression adjusted for the number of relapses in the year prior to study entry as well as baseline EDSS score and age." We suggest changing "number of relapses in the year prior to study entry" to "baseline relapse rate," which was not determined solely by prior year but rather the number of relapses in the 3 years before study entry divided by 3. Also need to add adjusted for prior IFNbeta use.

Page 28: The report states "There were significant improvements in quality of life as measured by the MSIS-29 physical score and the EQ-5D summary health index for daclizumab compared to placebo. There were also statistically significant improvements on the MSFC at 96 weeks (0.091 vs. 0.055, p<0.001) as well as its components, the timed 25-foot walk, the 9-hole peg test, and the 3-second paced auditory serial addition test." It is not clear if you

are limiting the information to pre-specified list of outcomes or including all statistically significant outcomes. If the latter, we suggest you also add MSIS PSYCH, EQ-VAS, and SDMT.

Pages 39-45: The NMA for disability progression should include the 24-week CDP for daclizumab.

Page 40: The report states "…and the DECIDE study of daclizumab versus interferon beta-1a 30 mcg (RR 0.79 and 0.84)." The RR for daclizumab should be 0.73, not 0.79.

Page 47: The report states "Finally, in the daclizumab trials there were significant differences between the daclizumab 150 mg group and the placebo group in the MSIS-29 physical impact score, but not the psychological impact score." However, MSIS-29 PHYS was not statistically significant within the sequential closed testing procedure.

Page 47: Table 11. Harms of DMTs: It is unclear how these percentages were derived. Hepatic injury data is from SELECT, autoimmune hepatitis data is from integrated analysis, and not sure about immune-reactions (PI has 4% for DECIDE and 0.5% for SELECT). Would suggest using the pooled data included in the prescribing information for each DMT. The D/C rate for daclizumab is listed as 15% . What is the source for this? Is this supposed to be D/C rate due to AEs? SAEs? What is the source for the 22% SAE?

Page 48 Table: For fair balance, a disclaimer statement should be added such as "Since ocrelizumab is not yet FDA-approved, it is not known if it will have a black box warning." Ocrelizumab clinical trial data also shows higher death rates and higher malignancy rate vs. placebo. These should be included in the table.

Page 50: In paragraph 3, the report states that only one of the 39 reviewed RCTs studied a population that had received at least one prior treatment with a DMT. Both daclizumab pivotal trials included patients with previous DMT experience. Are these really the only two studies that included MS patients who received at least one prior treatment with a DMT?

Pages 51-52, 54: There needs to be more transparency around the objective criteria that differentiate a moderate to large net health benefit and incremental or better net health benefit and the ICER rating on the comparative net health benefit of newer DMTs for RRMS compared to the interferons and glatiramer acetate.

Pages 58-59: Cost-Effectiveness Model: Methods: The RRMS model is based on treatment-naïve RRMS patients starting on any of the included DMTs as first line, then switching to a second line agent, then transitioning to best supportive care. This is not consistent with current clinical practice, payer coverage policies, or the labeled indication for some of the DMTs. The model does not seem to take into consideration the impact of DMT sequencing (the use of a higher efficacy agent after failure of interferon beta or glatiramer acetate). Both Zinbryta and Lemtrada are generally reserved for use after failure of 2 or more DMTs and payer coverage policies generally restrict use accordingly, so it may not be appropriate for Zinbryta and Lemtrada to be included in the model as first line agents. Additionally, in clinical practice, patients who fail a second DMT move to subsequent therapies; they do not move to supportive care. In a 2009 retrospective analysis of 606 patients with relapsing forms of MS taking a DMT, the average time for those patients who switched DMTs was 3.4 years after DMT initiation. *Teter B, Agashivala N, Kavak K, Chouhfeh L, Hashmonay R, Weinstock-Guttman B. Characteristics influencing therapy switch behavior after suboptimal response to first-line treatment in patients with multiple sclerosis. Mult Scler. 2014;20(7):830-836.* According to a market research study of 2,374 patients, an MS patient is on initial DMT therapy an average of 4.1 years before transitioning to a second line DMT and the time of second switch is on average 3.4 years later. *Data on file H16.DoF.033.*

Page 61: Table 15. Key Model Assumptions: The model assumes that the DMT discontinuation rate was constant for all DMTs and EDSS levels. While clinical trial data may not represent real world discontinuation rates, it is not appropriate to assume all DMTs have the same discontinuation rate. The model also assumes that second-line treatment was evenly distributed across natalizumab, fingolimod, and alemtuzumab. Both Zinbryta and Lemtrada are generally reserved for use after failure of 2 or more DMTs and payer coverage policies generally restrict use accordingly. What is the rationale for including Lemtrada but not Zinbryta as a second line agent in the model? The model also assumes that patients who discontinued on second-line treatment were assumed to follow the natural history progression of disease. Again, in clinical practice, patients who fail a second DMT move to subsequent therapies; they do not move to supportive care. This assumption results in the natural progression of disability and the associated costs being built into the model for all patients after failure of 2 DMTs, which is not seen in the real world.

Page 64 & Page 154: Table E4: Again, most of the MS DMT clinical trials were relatively short duration and some new adverse events were identified through post-marketing surveillance, so the SAE rates from the prescribing information should be used, rather than clinical trial data alone, for a more accurate picture of the safety profiles of the DMTs and to better estimate costs associated with SAEs.

Page 65: Drug Acquisition Costs – More transparency about the methodology used by SSR Health to calculate (discounted) drug acquisition costs is necessary; a cost-effectiveness model should be able to be replicated.

Page 65: "For alemtuzumab, costs were applied as calculated for year 1 and year 2. For years 3-5, the year 2 cost was applied to 19%, 13%, 16%, and 9% of patients who received an additional course in that year". Why are there four percentage numbers for the 3rd, 4th and 5th year? How is alemtuzumab modeled after year 5? Do they go to natural progression or second line DMT? This has a significant impact on cost-effectiveness.

Page 66: Table 19. DMT Acquisition Costs – More transparency is needed about the DMT Acquisition Cost for Year 1 and subsequent years. Are drug administration and monitoring costs built in? Are SAE costs built in? Please update the costs for Avonex, Betaseron, Extavia, Rebif, and Plegridy using the annualized methodology suggested for Page 9, Table 1.

- Interferon B-1a (Avonex): $62,968 (not $60,705) – Calculation: [WAC x (365/28)] x (1-20%)
- Interferon B-1b (Betaseron): $52,692 (not $44,993) - Calculation: [6218.71 x (365/28)] x (1-35%)
- Interferon B-1b (Extavia): $43,956 (not $37,533)- Calculation:[5558.21 x (365/30)] x (1-35%)
- Interferon B-1a (Rebif): $69,624 (not $66,153) – Calculation: [6283.57 x (365/28)] x (1-15%)
- Peginterferon B-1a (Plegridy): $68,292 (not $65,715) – Calculation: [5821.00 x (365/28)] x (1-10%)

Page 67: The report states that all drug monitoring costs for alemtuzumab are directly billed to the manufacturer by the laboratory. However, the manufacturer is not permitted to pay drug monitoring costs for Medicare patients. Therefore, some monitoring costs should be built into the model.

Page 67: Annual Costs by EDSS State - How were the indirect and direct costs for EDSS state extrapolated from the equations: Direct cost= 4427.7*EDSS + 27443; Indirect cost = 1594.1* EDSS +2,217.5 to get the direct cost for EDSS=0 $2825 and indirect cost $10,711?

Page 69-75: Cost-Effectiveness Model: Results - The model should be run again, using the accurate annualized pricing for the beta interferons.

Pages 77-80: Potential Budget Impact Model: Methods - The report states that they assumed a lower uptake for daclizumab based on its relatively modest effectiveness, its likely use mainly in JC virus-positive patients, and its potential displacement of only one other drug (natalizumab). This is not consistent with the comparative effectiveness results from the NMA, which shows Zinbryta as the most efficacious self-administered DMT. There needs to be greater transparency around the assumption that daclizumab is only displacing natalizumab in JC virus-positive patients. This is not consistent with clinical practice or physician market research that has been conducted. Additionally, the uptake (10% market share) may be overstated if the assumption is that daclizumab would only displace natalizumab in JC virus-positive patients. **Page 80: Table 25:** The eligible population is overstated. The number in the table reflects the number of diagnosed MS patients in the U.S., not the number of treated MS patients. DMT treatment rate in the first 2 years after diagnosis of MS is only about 67%. *Milliman, April 2016 Multiple Sclerosis: New Perspectives on the Patient Journey.* Additionally, the market share of natalizumab patients who are JC virus-positive does not likely equate to 10% of the MS market.

Comments on the Voting Questions:

Questions 4, 5 etc.: There is no head-to-head trial between these products and there are many limitations to the NMA & comparative effectiveness model. Therefore, there is not enough evidence to make "Yes or No" determinations. We request the question be restated as "Better than, Similar to, or Worse than". Currently, if the answer is "No", it could mean both "similar to" or "worse than".

Question 4. Zinbryta should be both Biogen Inc. and AbbVie Inc.

Question 4 compares daclizumab against fingolimod and dimethyl fumarate in terms of clinical effectiveness, but for long term value for money, **Question 8** compares daclizumab Glatopa. Shouldn't the same comparator be used for both questions?

December 21, 2016

Matt Seidner
Program Manager
Institute for Clinical and Economic Review
2 Liberty Square, 9th Floor
Boston, MA 02109
Ph. 617-528-4013, x7008
mseidner@icer-review.org
www.icer-review.org

Re: Draft Evidence Report on Treatments for Multiple Sclerosis

Bayer Pharmaceuticals ("Bayer") appreciates the opportunity to submit comments on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report entitled "Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value."[1]

Becky Germino
Assistant Director
US Data Generation and
Observational Studies
Bayer Corporation
100 Bayer Blvd.
Whippany, NJ 07981-0915
Tel: (862) 404-5830
Email: becky.germino@bayer.com

Bayer has more than 12,000 employees across the United States and is a global life science company with more than 150 years of experience researching and developing new pharmaceuticals and medical devices. We focus our efforts where we can have the most beneficial impact on the lives of those who depend on our innovative products. Our mission is to discover and manufacture products that will improve human health worldwide by diagnosing, preventing and treating diseases.

We commend ICER for conducting this evaluation to further shed light on the clinical benefits, safety, and cost effectiveness of these drugs. We also recognize that a comparison across the multitude of products approved for MS is potentially problematic with an almost complete lack of comparative data. Thus, we applaud ICER in its attempt to address these issues in a robust and methodologically sound way, while also seeking to further improve upon the draft that has been shared. In that spirit, we would like to offer our recommendations in this letter:

1. *The Topic in Context*

In the discussion of the "Topic in Context" the ICER draft noted that it did not review studies in patients with clinically isolated syndrome (CIS). However, the report goes on to say, "…many patients with CIS never go on to MS, so the results are not directly applicable to the role of DMTs in RRMS."

---

[1] Institute for Clinical and Economic Review. "Draft Evidence Report: Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value." November 22, 2016.

We believe it is important that ICER mention that there are several publications that look at predictors of the progression from CIS to RRMS which may provide interesting context to this issue. Multiple studies have also been undertaken to assess the impact of early DMT treatment (pre-diagnosis of clinically definite MS) on long-term health outcomes and progression of disease. Thus, the statement from ICER is somewhat misleading as it seems to imply that there is no evidence to support the use of DMTs in CIS patients (despite the fact that the FDA has approved CIS indications for several DMTs) or which CIS patients are more likely to progress and therefore appropriate candidates for early treatment.

2. *Table 4: Representative Private Payer Policies for MS DMTs*

Currently, Table 4 combines Betaseron and Extavia as part of the coverage policy description for Interferon β-1b 250 mcg. However, there are differences in the way these products are covered. For example, in the reference cited by ICER for Anthem BCBS, Betaseron is listed as tier 4 with a prior authorization (PA) but Extavia is listed as Tier 5 with a PA (see the notes column page 72 and 73). We feel it would be more appropriate to list these separately rather than grouping these together as specialty. Betaseron and Extavia have different injectors, syringe sizes (27G vs 30G), and support programs and, furthermore, are covered differentially by insurance companies and thus should be considered separately in this table.

3. *Table 11: Harms of DMTs*

In Table 11, ICER notes that "flu-like symptoms are common." However, it is recommended that the descriptor be revised to "flu-like symptoms are common (57%) but the incidence decreased over time with 10% of patients reporting flu-like symptom complex at the end of studies" to reflect the language in the product label.

4. *Limitations*

In the scoping document, many clinical and quality of life related outcomes were listed as outcomes of interest. While we understand that these cannot be included in the network meta-analysis, the scoping document promised a descriptive evaluation of these outcomes. However, there is little to no discussion of these additional outcomes for each product under review despite the existence of supportive evidence. This should both be added as a limitation of the review (as the benefit of products assesses only relative risk of relapse and progression of disease) and addressed descriptively for each product under review that has supportive evidence on the outcomes of interest reported in the scoping document. This is particularly critical in our opinion for those long-term outcomes such as survival, productivity, and progression to SPMS.

Sincerely,
Becky Germino
Assistant Director
US Data Generation and Observational Studies
Bayer Corporation

<u>References</u>

Achiron A, Barak Y. Multiple sclerosis-from probable to definite diagnosis: a 7-year prospective study. *Arch Neurol*. 2000;57(7):974-979.

Boggild M, Palace J, Barton P, et al. Multiple sclerosis risk sharing scheme: two year results of clinical cohort study with historical comparator. *BMJ*. 2009;339:b4677.

Brettschneider J, Petzold A, Junker A, Tumani H. Axonal damage markers in the cerebrospinal fluid of patients with clinically isolated syndrome improve predicting conversion to definite multiple sclerosis. *Mult Scler*. 2006;12:143-148.

CADTH Therapeutic Review. Recommendations for drug therapies for relapsing-remitting multiple sclerosis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2013 Oct;1(2C).

Clerico M, Faggiano F, Palace J, Rice GPA, Tintorè Subirana M, Durelli L. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. *Cochr Datab Syst Rev*. 2008(2).

Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomized study. *Lancet*. 2001;357(9268):1576-1582.

Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;374(9700):1503-1511.

Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. *N Engl J Med*. 2000;343:1430-1438.

Coyle PK. Early treatment of multiple sclerosis to prevent neurologic damage. *Neurology*. 2008;71(suppl 3):S3-S7.

Edan G, Kappos L, Montalban X, et al. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. *J Neurol Neurosurg Psychiatry*. 2014;85:1183-1189.

Fahrbach K, Huelin R, Martin AL, Kim E, Dastani HB, Rao S, Malhotra M. Relating relapse and T2 lesion changes to disability progression in multiple sclerosis: a systematic literature review and regression analysis. *BMC Neurol*. 2013 Nov 19;13:180.

Feuillet L, Reuter F, Audoin B, et al. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Mult Scler*. 2007;13:124-127.

Filippi M, Rovaris M, Inglese M, et al. Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomized, double-blind, placebo controlled trial. *Lancet*. 2004;364:1489-1496.

Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNbeta-1b trial. *Neurology*. 2012a;78(17):1315-1322.

Goodin DS, Ebers GC, Cutter G, et al. Cause of death in MS: long-term follow-up of a randomised cohort, 21 years after the start of the pivotal IFNbeta-1b study. *BMJ Open*. 2012b;2(6).

Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med*. 2000;343(13):898-904.

Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology*. 2006;67(7):1242-1249.

Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3 year follow-up analysis of the BENEFIT study. *Lancet*. 2007;370:389-397.

Kappos L, Freedman MS, Polman CH, et al. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. *Lancet Neurol*. 2009;8:987-997.

Kappos L, Edan G, Freedman MS, et al. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. *Neurology*. 2016 Sep 6;87(10):978-987.

Kinkel RP, Kollman C, O'Connor P, et al. CHAMPIONS Study Group. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. *Neurology*. 2006;66(5):678-684.

Kinkel RP, Dontchev M, Kollman C, et al. Association between immediate initiation of intramuscular interferon beta-1a at the time of a clinically isolated syndrome and long-term outcomes. *Arch Neurol*. 2012;69(2):183-190.

Marcus JF, Waubant EL. Updates on clinically isolated syndrome and diagnostic criteria for multiple sclerosis. *Neurohospitalist*. 2013 Apr;3(2):65-80.

Masjuan J, Alvarez-Cermeno JC, Garcia-Barragan N, et al. Clinically isolated syndromes: a new oligoclonal band test accurately predicts conversion to MS. Neurology. 2006 Feb 28;66(4):576-578.

Miller D, Barkhof F, Montalban X, Thompson A, Filippi M. Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis. *Lancet Neurol*. 2005a;4:281-288.

Miller D, Barkhof F, Montalban X, Thompson A, Filippi M. Clinically isolated syndromes suggestive of multiple sclerosis, part II: non-conventional MRI, recovery processes, and management. *Lancet Neurol*. 2005b;4:341-348.

Montalban X, Kappos L, Freedman M, Hartung H, Edan G, Miller D, Polman C, Barkhof F, Stemper B, Hermann J, Stolz C, Sandbrink R, Pohl C, Pleimes D. Application of the Revised Versions of the McDonald Multiple Sclerosis 2010 Criteria: Retrospective Comparison using the BENEFIT Clinical Study Dataset. Presented at the 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Lyon, France. 10-13 October 2012.

Mowry EM, Pesic M, Grimes B, Deen SR, Bacchetti P, Waubant E. Clinical predictors of early second event in patients with clinically isolated syndrome. *J Neurol*. 2009;256(7):1061-1066.

National Multiple Sclerosis Society (NMSS). Clinically isolated syndrome (CIS). http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Clinically-Isolated-Syndrome-(CIS). Accessed September 27, 2016a.

National Multiple Sclerosis Society (NMSS). Diagnosing MS. http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-MS. Accessed September 27, 2016b.

National Multiple Sclerosis Society (NMSS). Treatments of CIS. http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Clinically-Isolated-Syndrome-(CIS)/Treatments. Accessed September 2016c.

Noyes K, Bajorska A, Chappel A, et al. Cost-effectiveness of disease-modifying therapy for multiple sclerosis: a population-based study. *Neurology*. 2011 Jul 26;77(4):355-363.

Palace J, Duddy M, Bregenzer T, et al. Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator. *Lancet Neurol*. 2015;14:497-505.

Pan F, et al. Long-term cost-effectiveness model of interferon beta-1b in the early treatment of multiple sclerosis in the United States. Clin Ther. 2012;34(9):1966-1976.

Penner IK et al. Effects of interferon beta-1b on cognitive performance in patients with a first event suggestive of multiple sclerosis. *Mult Scler*. 2012 Oct;18(10):1466-1471.

Tintoré M, et al. Baseline MRI predicts future attacks and disability in clinically isolated syndromes. *Neurology*. 2006 Sep 26;67(6):968-972.

December 21, 2016

Dr. Steve Pearson,

We appreciate the advancement of the discussion of value, which we think merits a thoughtful and holistic approach. Biogen has been a pioneer in the science of combatting the complex and debilitating problems of Multiple Sclerosis (MS), investing more than any other company in new therapies and taking bold steps to transform the way we treat MS today. Given our understanding of the heterogeneity of MS, we have provided the following comments and recommendations on ICER's Multiple Sclerosis Draft Evidence Review with the ultimate goal that physicians and patients have access to all treatments. The following comments pertain to perspective, lack of inclusion of patient reported outcomes and inaccuracies/inconsistencies with ICER's Final Scoping Document.

ICER's Approach Does Not Fully Capture Important Elements of Value (Perspective)

ICER's report on multiple sclerosis therapies is limited in its perspective. Because MS is complex, we believe the conversation should be about a broader impact and include more real world elements of value. The base scenario's inclusion of direct medical costs only does not include many aspects of value that are important to society. Societal benefits include the value to caregivers, the value to the healthy from having products available should they become sick, and the reduction/delay in co-morbid conditions due to delay in disease progression. Inclusion of these elements of value has shown to have a significant impact on the value of MS treatments[1-3].

Caregiver burden has been defined as the type of stress or strain that caregivers experience related to the problems and challenges they face as a result of the status of the care recipient[4]. As multiple sclerosis is a chronic, degenerative, neurological disease, the stress on caregivers will only increase as the disease progresses. There is a significant body of evidence on the impact of multiple sclerosis on patients' caregivers including impact on utility and quality of life [2,5,6]. We believe that any assessment of value of MS treatments must include utility decrements and quality of life changes of caregivers.

Recent research has also demonstrated that pharmaceutical interventions provide value to the population who are at risk of contracting a disease. Moreover, among persons at risk, this value rises with increasing impact of the disease[1,7]. The most current analysis demonstrates that for multiple sclerosis, a significant portion of the value to society was attributed to those who were at risk of multiple sclerosis due to risk aversion. The benefits to the healthy of MS treatment availability should be included in any value assessment.

Finally, research has demonstrated that multiple sclerosis is linked to many co-morbid conditions including depression, fatigue, mood swings, and irritability[8-9]. There is also recent evidence that demonstrates that increasing severity of MS is associated with increases in co-morbid conditions[3]. Therapies that delay progression could also delay the acquisition of co-morbid conditions. The current assessment of value does not incorporate these costs of co-morbid conditions. Incorporating the value of delaying co-morbid conditions should be included in any assessment of value.

ICER Excludes Important Published Data on Patient-Relevant Outcomes

ICER's selection of studies, which only included publications that either reported relapse rates or sustained disability progression, failed to recognize many important publications on quality of life, as these outcomes are typically reported in other publications than the main clinical trial publication. Our research indicates that the following outcomes have been measured in the listed clinical trials which meet the inclusion criteria.

SF-36	EQ5D Index	SF12	EQ5D VAS	MSIS-29
AFFIRM	ADVANCE	ADVANCE	CARE MS I	ADVANCE
CARE MS I	CONFIRM	SELECT	DECIDE	DECIDE
CONFIRM	DECIDE		FREEDOMS II	SELECT
DEFINE	DEFINE		SELECT	
TOWER	FREEDOMS II			
	SELECT			
	TEMSO			

We believe that patient reported outcomes are important in treatment decisions and should be incorporated in an assessment of comparative effectiveness.

Multiple Inaccuracies and Inconsistencies in ICER's Analysis and Recommendations

Population

ICER's final scoping document stated that this analysis was done for treatment naïve patients. There are inconsistencies between the current analysis and the stated scope.

- According to the indication statement for both Daclizumab[10] and Alemtuzumab[11], due to their safety profile, the usage of these products should generally be reserved for patients who have had inadequate response to two or more drugs indicated for the treatment of MS. As this review is for treatment naïve patients, these two products should not be included in the analysis.
- Irrespective of indication statement, the CARE-MS II[12] trial consisted solely of patients who were previously treated with either interferon or glatiramer acetate. Because there were no treatment naïve patients in this trial, it should be excluded from the analysis of effectiveness.

Annualized Relapse Rate (Table C4)

ICER's final scoping document states that "Evidence on intervention effectiveness was derived from studies of at least one year's duration." The following trials do not meet the minimum 1-year duration criteria, which is inconsistent with the scope and should be excluded from the final analysis

- Comi, 2001[13] comparing glatiramer acetate 20mg daily to placebo is of **9 months duration**
- Panitch, 2002[14], the EVIDENCE trial comparing interferon beta 1-a 44mcg TIW to interferon beta 1-a 30mcg once weekly is of **6 months duration**
- Saida 2012[15] comparing fingolimod 0.5 mg once daily to placebo is of **6 months duration**
- O'Connor 2006[16] comparing Teriflunomide 7 mg once daily, Teriflunomide 14 mg once daily and placebo is only of **8 months duration**
- Kappos 2011[17] comparing Ocrelizumab 600 mg IV every 6 months, interferon beta 1-a 30 mcg IM once weekly and placebo is of **8 months duration**

The ICER report states that it "limited the review to the doses that match the FDA-approved indication except for drugs that do not have a current FDA indication for MS." The following trials/products do not meet this criteria and should be excluded from an analysis of effectiveness

- Rituximab 1000 mg IV is not approved for use in patients with multiple sclerosis and has no on-going trials in multiple sclerosis seeking approval.
- The OWIMS 1999[18] trial was a comparison of interferon beta 1-a 22 mcg once weekly, interferon beta 1-a 44 mcg once weekly and placebo.

The following list of technical inaccuracies/inconsistencies in the draft evidence review should be corrected for the final review

- The actual number of relapses reported in the Etemadifar 2006[19] trial is as follows:
  - 65 relapses for the Betaferon group
  - 66 relapses for the Rebif group
  - 57 relapses for the Avonex group
  These values have been misreported in Table C4. Given that these values and the reported number of patient years are in the same publication, the annualized relapse rates should be changed.

- There are additional inconsistencies with reporting of annualized relapse rate in Table C4 with data reported in the literature

- The annualized relapse rate in the IFNB MS study[20] as reported in the original publication was interferon beta 1b 0.84 vs placebo 1.27 after two years. Please correct in the final report.
- The annualized relapse rate in the interferon beta 1-a arm of the DECIDE[21] trials should be 0.4 at 2 years.
- The annualized relapse rates for the OPERA I[22] trial are 0.156 for the Ocrelizumab arm and 0.292 for the interferon beta 1-a (Rebif 44mcg) arm.

Disability Progression (Tables C5 & C6)

For the analysis of disability, allowing inclusion of dichotomous data from different time points introduces bias. By not incorporating time through hazard ratios, the analysis is inherently biased by allowing certain trials to only account for one year of disability progression whereas other trials allow for double the amount of time at two years. This could essentially double the number of patients who progress in certain trials. Furthermore, as stated in our response to the draft scoping document, the combination of disability progression at 12 weeks and 24 weeks is essentially combining two separate endpoints. Given that disability progression can be temporary and caused by the residual effect of a relapse, a more robust measure is confirmed disability progression (CDP) over a six month (24 week) interval rather than a 3 month (12 week) interval[23]. We again recommend that only confirmed disability progression at 24 weeks measured at 2 years be the sole endpoint used to measure disability progression.

Consistent with the inaccuracy of including trials of less than one year in length in the analysis of annualized relapse rate, the following trials should be excluded from an analysis of effectiveness:

- Panitch 2002, the EVIDENCE[14] trial comparing interferon beta 1-a 44 mcg TIW to interferon beta 1-a 30 mcg once weekly is of **6 months duration**

Allowing for the inclusion of the EVIDENCE[14] trial also introduces an inconsistent network. Using the point estimates of the CombiRx[24] trial demonstrates that interferon beta 1-a 30 mcg has less disability progression than glatiramer acetate 20 mg. The REGARD[25] trial demonstrates that glatiramer acetate 20 mg has less disability progression than interferon beta 1-a 44mcg. Including the EVIDENCE trial would support that interferon beta 1-a 44 mcg has less disability progression than interferon beta 1-a 30 mcg creating inconsistency within the network. Given that it doesn't meet the inclusion criteria and creates an inconsistent network, the EVIDENCE trial should be excluded from the analysis.

The following are additional technical inaccuracies/inconsistencies with Tables C5 & C6 which should be corrected in the final report.

- There are no values for Calabresi 2014[26] comparing peg-interferon beta 1-a 125 mcg to placebo, yet this product was included in the analysis. For transparency, these values should be included in Table C5.

- As stated in our response to ICER's data request, the hazard ratio in the AFFIRM[27] trial for CDP24W comparing natalizumab 300 mg to placebo is 0.46 and not 0.58. For an accurate representation of Natalizumab, this should be corrected in the final report.
- The CARE MS II[12] study comparing Alemtuzumab 12 mg to interferon beta 1-a 44 mcg is solely previously treated patients and should be excluded from an analysis of treatment naïve patients.
- The hazard ratio for CDP24W in the DECIDE[21] trial comparing Daclizumab 150 mg to interferon beta 1-a 30 mcg is 0.73. For accurate representation of Daclizumab, this should be corrected in the final report.

Summary

Biogen is a leader in researching and developing multiple sclerosis therapies. Through our own research on comparative effectiveness and the value of our therapies, we have made recommendations to ensure that ICER's report of multiple sclerosis therapies represents a true comparative assessment of value. These recommendations include expanding the perspective to include more real world assessments of value and to incorporate caregiver burden, the value to the healthy and the benefits of delaying disability and its effect on co-morbid conditions.

We further recommend the inclusion of patient reported outcomes in any assessment of comparative effectiveness and have provided evidence of existing data allowing for such a comparison.

Finally, there are inaccuracies and inconsistencies in ICER's draft evidence review of multiple sclerosis therapies which should be corrected in the final report. Without correction, the current review introduces significant heterogeneity and biases in comparative effectiveness influencing the assessment of value.

Dennis M. Meletiche
Vice President, Global Health Economics & Outcomes Research

References

1. Shih T, Wakeford C, Meletiche D *et al.* Reconsidering the Economic value of Multiple Sclerosis Therapies. American Journal of Managed Care. 2016 Oct; 22(11):e368-e374.
2. Kobelt G, Berg J, Lindgren P *et al.* Costs and Quality of Life of Patients with Multiple Sclerosis in Europe. Journal of Neurology Neuroscience and Psychiatry. 2006 Aug;77(8):918-926.
3. Pyenson B, Han F, Fredericks M *et al.* Multiple Sclerosis: New Perspectives on the Patient Journey. Milliman Client Report. Accessed December 15, 2016. http://us.milliman.com/uploadedFiles/insight/2016/multiple-sclerosis-new-perspectives.pdf
4. Buhse M. Assessment of Caregiver Burden in Families with Multiple Sclerosis. The Journal of Neuroscience Nursing. 2008 Feb;40(1):25-31.
5. Gupta S, Goren A, Phillips A *et al*. Self-reported Burden Among Caregivers of Patients with Multiple Sclerosis. International Journal of MS Care. 2012 Winter;14(4):179-187.
6. Buchanan R, Radin D & Huang C. Caregiven Burden among Informal Caregivers Assisting People with Multiple Sclerosis. International Journal of MS Care. 2011 Summer;13(2):76-83.
7. Lakdawalla D, Malani A & Reif J. The Insurance Value of Medical Innovation. National Bureau of Economic Research Working Paper 21015. Issued March 2015.
8. Seigert R & Abernathy D. Depression in Multiple Sclerosis: A Review. Journal of Neurology Neuroscience and Psychiatry. 2005;76:469-475.
9. Janardhan V & Bakshi R. Quality of Life in Patients with Multiple Sclerosis: the Impact of Fatigue and Depression. Journal of the Neurological Sciences. 2002 Dec;205(1):51-58.
10. Daclizumab USPI. Accessed on December 19, 2016. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761029s000lbl.pdf
11. Alemtuzumab USPI. Accessed on December 19, 2016. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103948s5139lbl.pdf
12. Coles AJ, Twyman CL, Arnold DL, *et al.* Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012;380(9856):1829-39.
13. Comi G, Filippi M, Wolinsky J. European/Canadian Multicenter, Double-Blind, Randomized, Placebo-controlled study of the Effects of Glatiramer Acetate on Magnetic Resonance Imaging Measured Disease Activity and Burden in Patients with Relapsing Multiple Sclerosis. Annal of Neurology 2001;49(3):290-297.
14. Panitch H, Goodin DS, Francis G, *et al.* EVidence of Interferon Dose-response: Europian North American Compartative Efficacy, University of British Columbia MS/MRI Research Group. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology 2002;59(10):1496-506.
15. Saida T, Kikuchi S, Itoyama Y *et al.* A Randomized Controlled Trial of Fingolimod (FTY720) in Japanese Patients with Multiple Sclerosis. Multiple Sclerosis. 2012;18(9):1269-1277.

16. O'Connor P, Li D, Freedman M *et al.* A Phase II Study of the Safety and Efficacy of Teriflunomide in Multiple Sclerosis with Relapases. Neurology. 2006;66(6):894-900.
17. Kappos L, Li D, Calabresi P, *et al.* Ocrelizumab in relapsing-remitting Multiple Sclerosis: A phase 2, Randomised, Placebo-Controlled, Multicentre Trial. Lancet. 2011;378(9805):1779-1787.
18. Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. Neurology 1999;53(4):679-86.
19. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand 2006;113(5):283-7.
20. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993;43(4):655-61.
21. Kappos L, Wiendl H, Selmaj K, *et al*. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2015;373(15):1418-28.
22. Hauser S, Comi G, Hartung P, *et al.* Efficacy and Safety of Ocrelizumab in Relapsing Multiple Sclerosis - results of the interferon-beta-1a-controlled, double-blind, Phase III OPERA I and II studies. Paper presented at ECTRIMS 2015. Barcelona Oct 9.
23. Wiendl H, Meuth SG. Pharmacological Approaches to Delaying Disability Progression in Patients with Multiple Sclerosis. Drugs. 2015 Jun;75 (June, 2015): 947-977.
24. Lublin FD, Cofield SS, Cutter GR, *et al*. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. Annals of Neurology 2013;73(3):327-40.
25. Mikol DD, Barkhof F, Chang P, *et al*. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol 2008;7(10):903-14.
26. Calabresi PA, Kieseier BC, Arnold DL, *et al*. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurology 2014;13(7):657-65.
27. Polman CH, O'Connor PW, Havrdova E, *et al*. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354(9):899-910.

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor   December 21, 2016
Boston, MA 02109

Dear Dr. Pearson,

EMD Serono, Inc., appreciates the opportunity to provide feedback on the Institute for Clinical and Economic Review's (ICER) draft evidence report, "Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value." EMD Serono, the North American biopharmaceutical business of Merck KGaA, Darmstadt, Germany, develops and offers therapies for disease areas including multiple sclerosis, infertility and cancer.

EMD Serono recognizes that providing high value therapies to patients is important to individual patients, clinicians, payers, and the health system at large, and appreciates ICER's contribution to the dialogue. Due to the importance of this discussion, EMD Serono would like to highlight how critical it is for ICER's report to rely on an approach that incorporates key stakeholder perspectives to facilitate use for sound value assessment.

Additionally, it is important to note that the findings of this value assessment may be interpreted differently by each of the stakeholder groups who may use, or be influenced by, these tools. Below, we outline three areas of concern with the ICER's draft evidence report and respectfully request ICER to consider these concerns.

1. Lack of Patient-Centric Focus and Measures

ICER acknowledges that there is a "mismatch between concepts and terms used to describe value across patients, clinicians, innovators, and payers" and rightly states that "patients should be at the center of the discussion."[1] However, the current draft report focuses on cost-effectiveness and budget impact - it is clear that the intent of the report is solely from the perspective of the payer. While we applaud the steps ICER has taken to solicit patient input in the generation of this report (ICER Report, p.13), it is unclear how this input has been incorporated into the value assessment, and the lack of patient-centricity is starkly apparent in the heavy focus on system costs and short-term budget impacts as outputs of the value framework. This represents a movement away from the recognizable shift towards patient-centric and personalized medicine among policy-makers and regulators.[2]

In MS, where patient experience varies greatly and the condition can have severe impacts on day-to-day living, an aggregate evaluation approach is inappropriate, whereas a more nuanced approach is far more reflective of the needs of MS patients and the full value that innovative medicines offer in improving patients' ability to remain actively engaged in all aspects of their lives. EMD Serono encourages ICER to expand the range of benefits that are considered in the cost-effectiveness analysis to include more patient- and disease-specific measures. For example, recent literature affirms that patients value the ability to choose among different therapeutic options. The current report fails to formally capture patient-centric metrics such as ease of access, administration, choice, and patient peace of mind[3,4]. Within MS, studies have shown that early treatment following a diagnosis of RRMS can make a significant and positive impact on long-term outcomes.[10] Disease modifying therapies (DMTs) have been shown to reduce the rate of relapse, and with some therapies, slow disability progression[5]. The median age of onset for patients with MS is 30 years, striking patients as they are starting their careers and families.[9] The upfront costs associated with treatment can provide long-term benefits including increased productivity, improved quality of life, slowing of disability progression, and reduction in relapses.[9,11] The heavy focus on system costs, short-term budgets, and value to the "health system" rather than the benefits and costs actually borne by patients limits the utility of the draft report by de-prioritizing the interests of patients and elevating those of a diffuse "system" community. While a short-term impact analysis may be appropriate for a limited number of acute conditions, patients with RRMS are suffering from a long-term chronic disease, whose experiences may not be adequately appreciated when only short-term costs are considered as in the 5-year budget impact analysis.[6,7,8] As such, the five-year budget impact analysis reinforces the focus that many payers have on short-term costs at the expense of long-term patient health and well-being.

We therefore encourage ICER to more fully incorporate the feedback they have received from patient advocacy groups into its cost-effectiveness analysis. These groups can, and have, offered patient views on value and explorations of value beyond what is calculated into the quality-adjusted life year (QALY), especially as the use of QALY-based thresholds has been explicitly prohibited from being used by United States public payers in the Affordable Care Act (ACA)[9]. This more holistic view offered by patient advocacy groups would foster a more informed discussion on value than the current payer focus. An assessment that can be used collaboratively by patients, clinicians, and payers would contribute to "the conversation" more effectively than an assessment targeted solely at one stakeholder group.

2. Lack of Transparency and Methodological Limitations

While EMD Serono appreciates the efforts that ICER is making to improve transparency and inclusiveness in the value assessment process, there are several components that could be improved to ensure adequate input from all stakeholders.

Best practices have found that engaging key stakeholders continuously throughout the process ensures that the resulting scope and analysis are relevant to a broad range of users, while limiting investigator bias[10]. Policies made using ICER's evaluations now risk a narrow focus given all relevant stakeholders are currently not meaningfully included in the process. EMD Serono recommends that ICER allow for more input and stakeholder participation throughout the entire evidence report development process, and acknowledge how the feedback that ICER receives is incorporated into their analysis. As such, we suggest that ICER consider the following:

- provide opportunities for full participation during the entirety of the appraisal process;
  - o EMD Serono appreciated the opportunity to review and comment upon the cost-effectiveness model analysis plan; however, the detailed network meta-analysis (NMA), budget impact, and systematic literature review analysis plans were not made available until the release of this draft report, thus limiting the opportunity to provide review and comment of the analysis plans.
- make public the feedback received from all stakeholders, at all stages of the evidence report development process;
- take a sufficient amount of time to review these comments, re-evaluate relevant evidence, and incorporate necessary changes into the final report, including a point-by-point commentary of how each comment was considered and addressed. This type of approach typically occurs at other health technology assessment (HTA) agencies[11];
  - o EMD Serono has appreciated the opportunity to participate throughout this process and has provided extensive commentary and suggestions at each opportunity for interaction; however, based on a comparison of the initial model analysis plan with that which was included in the draft report, few of our suggestions have been incorporated, without any rationale as to why (i.e. our recommendation against conflating 3- and 6-month confirmed disability progression data in the NMA).
  - o To cite an additional example in more detail, EMD Serono reviewed the initial list of studies identified by ICER for the NMA and strongly recommended against the inclusion of data from the OWIMS study as this study evaluated Rebif once-weekly (qw) dosing administration, which is not an approved FDA dosing regimen for the RRMS indication. ICER is evaluating the Rebif thrice-weekly (tiw) dosing administrations and thus, the OWIMS study should be excluded to be consistent with the dosing regimen being evaluated; however, this study remains in the NMA (and is erroneously labeled as tiw dosing in the ICER Report, Tables C1-C6) and the OWIMS data continue to inform the network in the draft version of this assessment, leading to a bias of the analysis against Rebif.
- ensure a robust methodology review by (1) publishing the over-arching framework methodology in a respectable peer-reviewed journal; (2) publishing each framework per disease area - prior to preparing its scoping document – in a relevant peer-reviewed specialty journal to ensure the methodology is appropriate for the particular disease state; and (3) publishing the final report in an appropriate peer reviewed journal.
  - o For example, the ICER Ratings of Comparative Net Health Benefit (ICER Report, p.52) framework, which aims to summarize the relative efficacy and safety of each therapy, is qualitative and non-transparent. Surface under the cumulative ranking curve (SUCRA), a well-accepted and quantitative analytical framework for Bayesian NMAs[12], could have strengthened support for this analysis.

- o EMD Serono further believes that the methods in the draft report insufficiently includes the potential risks of each respective therapy, in part because safety outcomes have been poorly analyzed and reported by ICER. A mixed treatment comparison or an indirect treatment comparison could have been performed to more robustly evaluate the comparative safety risks associated with each product.

Further, the lack of supporting detail and transparency related to the assumptions made by ICER in the methods section of the draft report is a source of vulnerability for entry of bias into the analyses. As a specific example, ICER's use of SSR Health data as its basis for drug discounts is likely to result in an inaccurate measure of budget impact or cost-effectiveness for two reasons. First, the specific methods are not described (ICER Report, p.65) and the report lacks transparency into the calculations performed to arrive at the discount rate for each intervention. We cannot know, given the information provided, whether this approach incorporates numerous discounts, including mandatory discounts to Medicaid or 340B sales channels, or discounts to the DOD or VA. Secondly, drug discounts vary significantly from payer to payer; by failing to highlight this point in its results, ICER risks limiting the transferability of its findings to key payer audiences. For example, in the report's base case, despite comparable wholesale acquisition costs (WAC), Betaseron's net acquisition cost is 32% lower than Rebif's net acquisition cost (ICER Report, Table 19), which has a significant impact on the overall cost-effectiveness results for this pairwise comparison. EMD Serono recommends instead that WAC be used in the model's base case, with differing levels of discount applied to each intervention in a sensitivity analysis.

Additionally, although off-label use of therapies may be utilized to treat conditions, EMD Serono is concerned that ICER was unable to find extensive published literature and evidence for therapies that have yet to receive FDA approval for certain indications, as evidenced by the inclusion of Rituxan in the Scoping Document and NMA but its exclusion from the cost-utility model due to lack of usable disability progression data. As the body of evidence on both the costs and benefits of newer medicines increases over time, ICER's evaluation of emerging medicines may not adequately capture the true value of these interventions. EMD Serono recommends that ICER categorize any assessments of emerging therapies as preliminary, and schedule these medicines for reassessment as more evidence becomes available.

Along these lines, despite ICER's reported intention to focus on assessing effectiveness, the employed approach represents a missed opportunity to highlight the real-world value of therapies that have delivered a meaningful benefit to patients. Long-term outcomes data, such as that from PRISMS-15, has demonstrated that after 15 years, cumulative exposure to and long-term treatment with Rebif is associated with sustained efficacy on key measures of clinical disease activity[13]. Yet, these long-term studies are not considered in ICER's calculation of net health benefits. While the design of long-term extension studies may be associated with certain limitations, in this report ICER nonetheless highlights the benefits of other products that have different types of limitations in their evidence bases, given their lack of FDA approval, as highlighted above.

Finally, after discontinuation of an initial treatment, there is limited guidance on the sequence of therapies that may be used in the treatment of MS. The choice of subsequent therapy may depend on the reasons for stopping prior therapy. Thus, the decision to switch may depend on the history of the patient up to the point of discontinuation. In all cases, the impact of treatment switching on health outcomes and costs is complicated by the lack of trial evidence on the effect and safety of these therapies in a sub-optimally treated patient group. We therefore reiterate our concern with ICER's choice of approach in modelling treatment sequencing in MS, where all patients discontinuing first-line treatment will receive a weighted average of alemtuzumab / natalizumab / fingolimod in second-line. We do not believe that this assumption is supported by current DMT treatment patterns, as recent work has shown a large proportion of patients currently taking self-injectable DMTs (42.2%) had received one or more prior DMT treatment (ie., self-injectable or other)[14]. We also believe that it is inappropriate to consider alemtuzumab or daclizumab as first- or second-line treatment options for treatment-naïve patients, as the FDA recommends that both DMTs "should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS"[15,16]. We therefore believe it is not appropriate to exclude a switch to other treatment options (i.e., self-injectable or oral DMTs) in second-line.

3. Consistency and interpretation of results

Each of the beta-interferons is unique, in terms of their approved doses, frequency/mode of administration, efficacy, and safety. A well-controlled large, randomized, single blinded head-to-head trial of Rebif 44 mcg tiw and Avonex 30 mcg qw interferon formulations in RRMS (EVIDENCE) has demonstrated the superiority of Rebif 44 mcg tiw over Avonex 30 mcg qw on clinical efficacy, including proportion of patients without relapse, and MRI outcomes [17]. A statistically significant relapse benefit for Rebif 44 mcg qiw-treated patients has been demonstrated out to 16 months[18]. The strength of this evidence enabled the marketing of Rebif prior to the expiration of the orphan status exclusivity period of Avonex[19]. Based on the results of this study, other health services researchers, including the Drug Effectiveness Review Project, have concluded that "there is fair evidence that Avonex is less effective than Rebif for preventing relapse in patients with relapsing-remitting multiple sclerosis"[20]. ICER itself highlights in its report that "we judge there to be moderate certainty of a small-to-substantial net health benefit for Rebif compared to Avonex, with high certainty of at least a small net health benefit" (ICER Report, p.54-55), and indeed, the 95% credible interval for Rebif 44 mcg tiw versus Avonex 30 mcg qw from the NMA on annualized relapse rate (ARR) does not contain 1 (ICER Report, Table 6). It is therefore curious that, elsewhere in the report, the interferons are either grouped together indiscriminately on measures of efficacy (i.e., Figure 5), or no difference is found in their comparative net health benefit (ICER Report, Table 12 where both Rebif 44 mcg tiw and Avonex 30 mcg qw are rated by ICER as a "B"). EMD Serono recommends adjusting the report accordingly to correct the misrepresentation of these DMTs as identical to each other.

Second, researchers have suggested that, given that outcomes in MS are more based on disability than on life expectancy, a QALY-based incremental cost-effectiveness ratio (ICER) may not be a viable metric in this disease area[21]. As relapses are a key contributing factor to sustained disability progression[22], it has been suggested that the cost per relapse avoided should instead be considered as a more relevant measure of cost-effectiveness. On this endpoint, a wealth of prior research has shown the superiority of Rebif 44 mcg tiw over Avonex 30 mcg qw[23,24,25], when both short- and long-term horizons are considered. Cost per relapse avoided was considered in ICER's analysis, but its results were not highlighted in the report's conclusion. When considering ICER's analysis, Rebif 44 mcg tiw's ICER vs. Avonex 30 mcg qw is cost-effective with an ICER of $98,684 per relapse avoided (calculated from data in ICER Report, Table 21), a value that is in line with prior analyses.

Third, EMD Serono reiterates our concern with including OWIMS data in the NMA. OWIMS was a trial evaluating the efficacy of Rebif dosed qw versus placebo. No statistically significant impact on relapse or disability was demonstrated[26], and EMD Serono did not apply for FDA approval of this Rebif dosing regimen. The inclusion of this data in an analysis evaluating the comparative efficacy of Rebif dosed tiw is inappropriate and likely to significantly bias the results of the analysis against Rebif. We recommend that the analysis be adjusted to exclude data from the OWIMS study.

Fourth, EMD Serono recognizes the difficulties in conducting NMAs in MS, especially the likelihood and impact of heterogeneity. In part this may arise due to the period of time over which evidence has been generated in pivotal and other studies. In the case of the longer acting interferon (Plegridy), the least is known from only one placebo controlled study, with a study duration of 48 weeks. Inclusion of this one study with only 48-week data in the network for Plegridy, alongside other interferons with predominantly 96-week data from multiple studies, is likely to bias the results of the analysis in favor of Plegridy. There is also evidence comparing the interferons with glatiramer acetate through head-to-head studies (BEYOND, REGARD and COMBIRx), but no such comparison is available involving Plegridy that can inform the network, also likely biasing the results. In summarizing the cost-effectiveness results versus best supportive care (ICER Report, Table 23), ICER reports that Plegridy is a more cost-effective option than Rebif. Given the points we highlight concerning the evidence base for Plegridy, this conclusion cannot be qualified from the data presented.

Fifth, as we have highlighted in our prior feedback responses, we remain unclear on the reason why Rebif 22 mcg is the only interferon in the model for which serious AEs are accounted for (ICER Report, Table E4), given that Rebif 22 mcg has a similar adverse event profile to other interferon therapies (including the higher dose Rebif 44 mcg preparation, for which, counterintuitively, no serious adverse events are accounted for in the model). Along these lines, the risk of progressive multifocal leukoencephalopathy (PML) appears to only be accounted for with natalizumab, while post-marketing experience has also demonstrated a risk of PML with other treatments[27,28]. More generally, it is

unclear why ICER limits themselves to sourcing adverse events for the DMTs from clinical trial data, when many DMTs have a wealth of real-world safety data available, which could be used in addition to clinical trial data to inform the risk profile of DMTs in real clinical practice.

Sixth, ICER presents the results of their cost-effectiveness analysis versus two reference treatments: best-supportive care, and Glatopa. Payer decision-making relies on assessing the incremental benefits and costs of an intervention versus a current standard of care. We do not believe the current standard of care for treatment-naïve MS patients is adequately represented by ICER's choices of referent therapies, given that (1) recent evidence suggests that the majority of newly diagnosed patients in the United States are treated with a DMT[29] and (2) Glatopa is not the most-prescribed DMT in the United States[30]. We suggest revising the reference treatment in the cost-effectiveness analysis accordingly.

Finally, the NMA validation relative to existing literature, as well as the model's cost-effectiveness results, are presented in the main text tables and the conclusions section without any accompanying assessment of uncertainty, limiting their transparent interpretation. Early in the report, ICER itself highlights the limitations of indirect evidence: "The credible intervals for most of the drugs are quite wide, highlighting the limitations of indirect evidence to distinguish one drug or set of drugs from the others" (ICER Report, p.40). Indeed, when considering ICER's NMA results for disability progression (ICER Report, Table 9), the majority of self-injectable pairwise comparisons have 95% credible intervals that contain 1. ICER's use of Forest plots are open to misinterpretation: by arbitrarily placing one intervention higher than another in these figures, ICER implies rank-ordered meaningful differences in efficacy, when in fact the credible intervals are so wide that this conclusion would be unwarranted. Given that disability progression is a key model driver, and the point estimates from the NMA were used as model inputs in the base case, it is inappropriate to draw conclusions on cost-effectiveness based solely on the results of this deterministic analysis. This is underlined by the huge variability in the analysis results when deterministic and probabilistic sensitivity analyses are undertaken (ICER Report, Tables E11-16). EMD Serono suggests that (1) measures of uncertainty be presented in the main text tables as well as the report conclusions, and (2) language pertaining to 'superiority' be removed from the report, in order to better inform decision-makers with a fair view of the uncertainty of the evidence.

Conclusion

EMD Serono would like to emphasize that findings from this assessment could potentially – and in our opinion, mistakenly - be used to influence individual patient care. In the spirit of transparency, ICER should share use cases for how they see this information being utilized, as it is unrealistic to assume that this information will be used only at a theoretical population level and not trickle down to clinical decision-making. ICER should clarify that any assessments based on this Value Framework should only be used as an aid to stimulate discussion on the idea of value in healthcare from a broader population-based perspective. As the data used to develop the assessments are primarily drawn from population-based studies, ICER should explicitly clarify that value assessments based on this framework should not be used to guide clinical decisions or individual patient treatment plans. The American Academy of Neurology has "urge[d] access to all DMT for treating MS individuals when they have the potential to provide clinical benefit"[31]. Given the results from ICER's own NMA clearly show that all FDA-approved therapies reduce ARR relative to placebo (ICER Report, Table 6), EMD Serono strongly believes that under no circumstance should any result from this report be used to compromise patient access to treatment.

Prescription medicines offer a tremendous value to patients; this value should be captured through long-term analysis and a broad, comprehensive examination of risks and benefits. EMD Serono appreciates ICER's solicitation for comments to the draft evidence report and hope the final report includes a more robust incorporation of patient-centric measures, increased transparency related to methods and assumptions, and explicit consideration of the differences among the interferons. We strongly encourage ICER to be responsive to stakeholder input and to publish a revised report in a peer reviewed journal prior to use in decision-making. EMD Serono looks forward to continued engagement with ICER throughout this process.

Sincerely,
EMD Serono

References

[1] Institute for Clinical and Economic Review. Addressing the Myths About ICER and Value Assessment. Available at http://icer-review.org/wp-content/uploads/2016/08/icer_myths_facts.pdf.

[2] U.S. Food and Drug Administration. Guidance to Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009.

[3] Shingler SL, Swinburn P, Ali S, et al. A discrete choice experiment to determine patient preferences for injection devices in multiple sclerosis. J Med Econ. 2013 Aug; 16(8):1036-42.

[4] Shih T, et. al. Reconsidering the economic value of multiple sclerosis therapies. Am J Manag Care. 2016 Nov 1;22(11):e368-e374.

[5] Wiendl Hand Meuth S. Pharmacological Approaches to Delaying Disability Progression in Patients with Multiple Sclerosis. Drugs. 2015; 75(9): 947–97

[6] Ward BW, Schiller JS, Goodman RA. Multiple Chronic Conditions Among US Adults: A 2012 Update. Centers for Disease Control and Prevention Preventing Chronic Disease. April 2014, Vol 11.

[7] Kane RL, Priester R, Totten A. How the Current System Fails People with Chronic Diseases. Meeting the Challenge of Chronic Illness. American Society of Actuaries. 2005. Baltimore, MD.

[8] Frandsen BR, Joynt KE, Rebitzer JE, et al. Care Fragmentation, Quality, and Costs Among Chronically Ill Patients. Am J Manag Care. 2015;21(5):355-62.

[9] Weinstein M, Skinner J. Comparative Effectiveness and Health Care Spending — Implications for Reform. N Engl J Med 2010; 362:460-465.

[10] Buckley DI, Ansari MT, Butler M, et al. The Refinement of Topics for Systematic Reviews: Lessons and Recommendations from the Effective Health Care Program. J Clin Epi. 2014 Apr;67(4):425-32.

[11] National Institute for Health And Clinical Excellence. Guide to the single technology appraisal process. October, 2009. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Guide-to-the-single-technology-appraisal-process.pdf

[12] Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011;14(4):417–28. doi: 10.1016/j.jval.2011.04.00

[13] Kappos L et al. Factors influencing long-term outcomes in relapsing-remitting multiple sclerosis: PRISMS-15. J Neurol Neurosurg Psychiatry. 2015 Nov;86(11):1202-7. doi: 10.1136/jnnp-2014-310024. Epub 2015 Sep 15.

[14] EMD Serono. Data on file.

[15] Biogen. ZINBRYTA Prescribing Information. 2016.

[16] Genzyme. LEMTRADA Prescribing Information. 2016.

[17] Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology. 2002;59(10):1496-1506.

[18] Panitch H, et al. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. J Neurol Sci. 2005 Dec 15;239(1):67-74. Epub 2005 Sep 19.

[19] Rask C, Unger E, Walton M. Comparative study of Rebif to Avonex and orphan exclusivity [memorandum]. Department of Health and Human Services. 2002 March.

[20] Smith B, Carson S, Fu R, McDonagh MS, Dana T, Chan B, Thakurta S, Gibler A. Drug class review: Disease-modifying drugs for multiple sclerosis. Update 1. http://derp.ohsu.edu/about/final-products.cfm

[21] Mathis AS. Managed care aspects of managing multiple sclerosis. Am J Manag Care. 2013 Feb;19(2 Suppl):S28-34

[22] Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology. 2003 Dec 9;61(11):1528-32.

[23] Newton A, et. al. A Comprehensive Cost-Effectiveness Analysis of Treatments for Multiple Sclerosis. Int J MS Care. 2011 Fall; 13(3): 128–135.

[24] Goldberg LD, et. al. Comparing the cost-effectiveness of disease-modifying drugs for the first-line treatment of relapsing-remitting multiple sclerosis. J Manag Care Pharm. 2009 Sep;15(7):543-55.

[25] Guo, S. et. al. Treating relapsing multiple sclerosis with subcutaneous versus intramuscular interferon-beta-1a: modelling the clinical and economic implications. Pharmacoeconomics. 2009;27(1):39-53. doi: 10.2165/00019053-200927010-00005.

[26] The Once Weekly Interferon for MS Study Group. Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. Neurology. 1999 Sep 11;53(4):679-86.

[27] Biogen. TECFIDERA Prescribing Information. 2016.

[28] Novartis. GILENYA Prescribing Information. 2016.

[29] Hanson KA, Agashivala N, Wyrwich KW, Raimundo K, Kim E, Brandes DW. Treatment selection and experience in multiple sclerosis: survey of neurologists. Patient preference and adherence. 2014;8:415-22.

[30] IMS National Prescription Audit. October, 2016.

[31] American Academy of Neurology, 2015. POSITION STATEMENT: Availability of Disease Modifying Therapies (DMT) for Treatment of Relapsing Forms of Multiple SclerosisAvailable at: https://www.aan.com/uploadedFiles/Website_Library_Assets/Documents/6.Public_Policy/1.Stay_Informed/2.Position_Statements/DiseaseModTheraMS_PosStatement.pdf

Genentech
A Member of the Roche Group

December 21, 2016

Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

Dear ICER Review Panel:

Thank you for the opportunity to provide comments on the ICER draft report titled "Disease-Modifying Therapies for Relapsing Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value." This letter is in response to your request for comments relevant to the investigational drug product, ocrelizumab. We are concerned about errors and the lack of transparency of the methodology in different areas including the network meta-analysis (NMA) and economic models, for which Genentech was unable to replicate the results. Key areas that Genentech would like to address are correcting errors in the NMA of the annualized relapse rate (ARR), upgrading the ratings of ocrelizumab based on the publication of the manuscript, and deferring the economic evaluation of ocrelizumab until a price is available. Please see below for more details on our recommendations:

Key areas of recommendations:
Correct ocrelizumab's point estimate and 95% credible interval for the rate ratio of ARR in the NMA and re-check numbers in all NMAs, including subgroup analyses and meta-regressions. The corrected numbers should be reflected in the evaluation of the rating for ocrelizumab and the cost effective analysis.
- There was a discrepancy in the rate ratios for ARR between the OPERA trials and the ICER-conducted NMA, which is not typically observed between direct and indirect evidence.
  - The OPERA I and OPERA II trials compared ocrelizumab to IFNβ-1a 44mcg and a rate ratio of 0.54 and 0.53, respectively, was reported in the trials[1]; a much higher ratio of 0.66 was estimated in the NMA in the draft report (Page 37, Table 6), drawing questions on the face validity of the NMA.
  - In Genentech's attempt to replicate the NMA of ARR using ICER's methodology and the inputs listed on Table C4, our result for the rate ratio for ocrelizumab vs. placebo was 0.34 with a 95% credible interval of [0.27, 0.42], which is different than ICER's result of 0.43 [0.34, 0.54].[2]
  - We were able to replicate all other point estimates to +/- 0.02 for rate ratios of DMTs vs. placebo, except for ocrelizumab, in Figure 3.

- Given the short public comment period, we did not have sufficient time to replicate all the analyses, and request that the numbers for all NMAs should be verified, including the subgroup analyses and meta-regressions.

Conduct and add separate analyses for confirmed disability progression (CDP) at 12- and 24-week confirmation, as the two endpoints are not directly comparable.

Upgrade the quality of OPERA I and OPERA II trials from "fair" to "good" because all quality criteria have been met as described in ICER's quality criteria.
- In Table C3, the OPERA trials received an "Unclear" for "Comparable Groups." Please refer to Table 1 of the recently published manuscript for the baseline demographics and disease characteristics, which were similar between treatment groups in the two trials.[1]
- On page 28, The OPERA trials were judged to be of fair quality because they were *"presented in abstract form"* and *"due to relatively high loss to follow-up (14% and 18% respectively)."* The OPERA manuscript is now published and is enclosed for your review.[1] In addition, the percentage of patients lost to follow-up in the OPERA trials is comparable to other trials which meet the criteria for "Maintain Comparability", such as the FREEDOMS trial, which had a dropout rate of 19% and was judged to be of "good" quality (Table C3, Page 118).
- The quality and scientific rigor of study design should be considered in rating the quality of trials. OPERA I and OPERA II were the first double-blind, double-dummy active comparator trials with duration of two-years completed in MS. The trials had separate treating and examining investigators and central MRI readings, all blinded throughout the study.[1]

Upgrade the ocrelizumab rating from "B+" to "A" in both PPMS and RRMS (compared to best supportive care and compared to interferons and glatiramer acetate) based on ocrelizumab's benefit-risk profile compared to other DMTs and the availability of the manuscripts.
- In Genentech's attempt to replicate the NMA of ARR using ICER's methodology and inputs, our result for the rate ratio for ocrelizumab vs. placebo was 0.34 with a 95% credible interval of [0.27, 0.42], which is different than ICER's result of 0.43 [0.34, 0.54].[2] The corrected numbers should be reflected in the rating for ocrelizumab.
- Despite ICER's emphasis on benefit-risk of DMTs, ratings seem biased toward efficacy and it is unclear how potential harms were included.
  - Per the draft report, the evidence rating reflects a joint judgment on two components (Page 24): "Net health benefit" - the balance between clinical benefits and risks and/or adverse events, and level of certainty in the best point estimate of net health benefit.
  - Consider the data from Table 11 titled "Harms of DMTs" when incorporating risks into ratings for DMTs.

- Please update the text for RRMS regarding the rating of ocrelizumab on pages 51 and 53.
  - For RRMS, ocrelizumab was given a B+ rating because results have *"not yet been published"* and *"there is no real-world evidence supporting its efficacy"*. (Page 51, similar text on Page 53) The OPERA manuscript is now published and is enclosed for your review.[1]
  - The extent to which real-world evidence (RWE) informs ratings is inconsistent across DMTs and is not cited as a reason for a lower rating for other DMTs without RWE supporting efficacy.
- Please update the text for PPMS regarding the rating of ocrelizumab on page 55.
  - For PPMS, ocrelizumab was given a B+ *"due to the preliminary nature of the data"*. (Page 55) The ORATORIO manuscript is now published and is enclosed for your review.[3]
- The quality of clinical trials as measured by ICER using US Preventive Services Task Force (USPSTF) criteria should be considered in the ratings. It appears that "good" quality trials were not required for an "A" rating, for example, alemtuzumab received "A" rating with clinical trials that were rated as "poor" and "fair" in Table C3.

Defer the cost-effectiveness and budget impact modeling of ocrelizumab until ocrelizumab is FDA-approved and the price is available.

- Including a speculative price of ocrelizumab based on an arbitrary formula into a cost-effectiveness analysis or budget impact model is inappropriate and may be expected to result in misleading conclusions.

Provide clarity on the data source and methodology for the sales and utilization data used in the calculation of drug prices used in the draft report.

- Because ICER is using a third-party to obtain drug price, it is unclear how prices were derived and what they represent. We caution that the calculated drug price should not be stated as a definitive fact and that limitations to the analysis should be disclosed.

When ocrelizumab price is available, revise the PPMS budget impact model to assume a significant proportion of market uptake is replacement of off-label DMTs.

- In the draft report, potential budget impact of ocrelizumab was estimated based on incremental costs compared to best supportive care, but this does not reflect the current treatment patterns in PPMS.
- Based on data collected from 115 physicians, currently 53% of PPMS patients (N=215) are treated with DMT (see table 1 below) (Adelphi Multiple Sclerosis DSP V (Q1 2016), Data on file, 2016.)[4]
- Additional utilization data from a survey conducted in Spring 2015 among over 7,000 participants in the North American Research Committee on Multiple Sclerosis (NARCOMS) indicated that 33% of responders with PPMS were using an off-label DMT.[5]

- Therefore, assuming ocrelizumab will be replacing best supportive care will grossly overestimate its budget impact and therefore is misleading for payers. The revised report should instead assume a significant proportion of market uptake for ocrelizumab in PPMS is replacement of off-label DMTs.

Provide full disclosure and share the cost-effectiveness and budget impact models.
- We ask that the cost-effectiveness and budget impact models should be provided to stakeholders in a format facilitating feedback to increase confidence and credibility of ICER's evaluations. Genentech was not able to fully replicate the numbers in the cost-effectiveness analysis and budget impact analysis based on the current information in the report.
- The cost-effectiveness (CE) ratio of ocrelizumab vs. supportive care in PPMS from the probabilistic sensitivity analysis is $702,243 per QALY gained (Table E15, Page 172), whereas the deterministic CE ratio for ocrelizumab vs. supportive care in PPMS is $854,020 per QALY gained (Table 22, Page 72). The difference between these two results is fairly large and an explanation of this difference should be provided in the revised report.
- Please provide clarity in the final report on the budget impact analysis:
  - Does the calculation assume that all patients would initiate the therapy at the beginning of the year or initiate new therapy gradually over a 12 month period (e.g., patients initiating in December would only incur one month treatment during that year)?
  - How were costs estimated for patients when they enter the budget impact model in the first year vs subsequent years, for example, how were the 1st, 2nd, 3rd, 4th and 5th year costs estimated for those who initiated treatment in first year following entry? How were the 2nd, 3rd 4th and 5th year costs estimated for those who initiated treatment in the second year following entry, and so on?

Remove the arbitrary budget impact cap.
- The arbitrary budget cap ($904 million) for societal expenditures on medical innovation ignores the value of treatments and benefit to patients, caregivers, and society. Imposing an arbitrary budget cap for all new products can inadvertently stifle innovation particularly in areas of high unmet need, such as MS.

Include the following limitations of the NMA in the results section of the report:
- **Different assessment time points across trials:** Efficacy endpoints across various DMT trials occur at many different time points and may not be comparable across trials. If trial endpoints using different time points are analyzed, the assumptions of proportional hazards should be tested. For example, trials with a duration of 24 weeks will not provide meaningful CDP results due to the short duration of follow up.
- **Different definition of outcomes across trials:** The definition of key outcomes such as relapse rates and disease progression are heterogeneous across trials, which weakens the validity of indirect comparisons across trials.

- **Variable quality of clinical trials:** There is no consideration or weighting of the quality of the clinical trials, e.g. double-blinded vs unblinded, placebo-controlled vs open-label, which can introduce inconsistency across the network for comparisons.
- **Changes in natural history of disease over time:** The natural history of relapse rate has changed throughout the era of MS clinical trials, therefore comparing contemporary trials to those trials conducted a decade or more ago could result in differential background (and placebo) rates of relapse.[6] For example, a much higher ARR was reported for IFNβ-1a 44mcg in the PRISMS 1998 trial (ARR=0.87) and the OWINS 1999 trial (ARR=0.94) than that from other trials (ranging from 0.22 to 0.52). Inclusion of such trials would impact the estimates for both IFNβ-1a 44mcg and other treatments linked to IFNβ-1a 44mcg in the NMA.
- **Differences in baseline characteristics across trials:** The differences in baseline characteristics between different trials such as differences in age, baseline EDSS scores, number of prior therapies, disease duration, etc. may introduce biases into the results of the NMA. Meta-regression examines the impact of each characteristic separately but the collective impact of all these variables on the results of the NMA is difficult to assess.

Other recommendations and corrections:

In Table 1, add qualifier that there is no FDA-approved dose for rituximab in MS and correct the rituximab dose and associated whole-sale acquisition cost (WAC) to be consistent with MS clinical trials.

- In Table 1 under the "FDA-approved Dose" column, the stated dose for rituximab is 1000 mg every 6 months.
- In the Phase 1 open-label trial in RRMS, 26 patients received rituximab 1000 mg on days 1 and 15 totaling 2000 mg every 24 weeks.[7]
- In the Phase 2 single-dose proof-of-concept 48-week trial in RRMS, 69 patients received rituximab 1000 mg on days 1 and 15 totaling 2000 mg for one dose.[8]
- In the Phase 3 trial in PPMS, which failed to meet its primary endpoint, 292 patients received rituximab 1000 mg on days 1 and 15 totaling 2,000 mg every 24 weeks.[9]

In Table 11, correct safety information for rituximab to include safety data from clinical trials of rituximab in MS.

- Table 11 includes rituximab's major safety concerns from non-MS indications listed in the prescribing information for rituximab.
- Safety profiles will differ significantly based on disease state and background therapy and thus the draft report should list published safety information for rituximab from MS clinical trials.

Conduct sensitivity analysis of budget impact of ocrelizumab by varying prevalence of PPMS.

- The prevalence of PPMS is reported in literature ranging from 10-15%.[10] In the budget impact analysis, ICER used the higher end of the range (15%) and therefore a sensitivity analysis should be performed using lower end of the range to assess the impact on the overall budget impact.

In Table B2 titled "Ongoing Trials of Infused DMTs for MS", correct the comparator doses in the ocrelizumab trials and include additional ongoing trials

- In trials NCT01412333, NCT01247324 and NCT01194570, the doses of comparator arms are listed incorrectly.
  - For the OPERA I and II trials (NCT01412333, NCT01247324), the comparators are ocrelizumab 600 mg and IFN beta-1a (Rebif) 44 mcg.[1]
  - For the ORATORIO trial (NCT01194570), the comparators are ocrelizumab 600 mg and placebo.[3]
- Add the following ongoing Genentech-sponsored trials for ocrelizumab:
  - CHORDS[11]
  - CASTING[12]
  - VELOCE[13]
  - OBOE Biomarker Study[14]
  - Open-label extension of the Phase 2 study in patients with RRMS.[15]

Include health-related quality of life data for ocrelizumab in relapsing forms of MS and PPMS.

- In OPERA II, the difference in adjusted mean change in Short Form-36 (SF-36) physical component score was 0.69 in OPERA I (p=0.22) and 1.16 in OPERA II (p=0.04).[1]
- In ORATORIO, while ocrelizumab did not demonstrate a significant change in SF-36 physical component score compared with placebo (p=0.60)[3], post-hoc exploratory analyses, showed improvement on the SF-36 mental component score (p=0.0006) as well as reductions in fatigue as measured by the modified fatigue impact score (p=0.009).[16]

Include the OPERA I and OPERA II trials for the subgroup analysis that excludes trials with duration of <18 months for both ARR and CDP in Tables D1 and D5, respectively.

- For the subgroup analysis excluding trials with duration <18 months, the result is listed as "N/A" for ocrelizumab.
- The OPERA I and II trials had a duration of 22 months (96 weeks) and thus would qualify for this subgroup analysis.[1]

Correct additional errors listed in Appendix 1, organized by section of the report and page number.

We welcome the opportunity to provide clarification should ICER have questions on any of these points. Please contact Kyle Downey at downey.kyle@gene.com or (509) 344-9674.

Respectfully Submitted,

Jan Hansen, Ph.D.
Vice President, Evidence for Access
U.S. Medical Affairs, Genentech

APPENDIX 1. Additional recommendations, organized by section and page number

Section 1: Background		
Page	**Excerpt from ICER draft report**	**Genentech Recommendation**
2	"Several other agents have been studied for use in PPMS, but one – rituximab – is of particular interest to practitioners, patients, and insurers because its mechanism of action is similar to that of ocrelizumab, despite its lack of a labeled indication for MS."	Provide clarity for rituximab's lack of indication in PPMS: *"…due to the failure of rituximab to meet its primary endpoint in the trial for patients with PPMS."* [9]

Section 4: Comparative Clinical Effectiveness		
Page	**Excerpt from ICER draft report**	**Genentech Recommendation**
28	4.3 Results – RRMS Ocrelizumab "There was a 94-95% reduction in gadolinium-enhancing lesions in the two trials with ocrelizumab compared to interferon β-1a 44 mcg."	Add the p-value, $p<0.001$, for both trials.[1]
28-29	4.3 Results – RRMS Ocrelizumab "The number of new or enlarging T2 lesions was reduced with ocrelizumab (77% and 83% respectively, $p<0.0001$ for both trials) as was the reduction in the rate of brain volume loss (24% decrease in rate for both, $p<0.001$)."	1. Change p-value for new/enlarging T2 lesions to $p<0.001$ to align with the manuscript. [1] 2. To be consistent with manuscript, for brain volume loss, change to: *"The difference in rate of brain volume loss from Week 24 to 96 was 23% in OPERA I (p=0.004) and a 15% decrease in rate in OPERA II (p=0.09)."* [1]

29	4.3 Results – RRMS Ocrelizumab "SAEs, infections, and nervous system disorders were all lower in the ocrelizumab group."	Revise to "SAEs, including infections and nervous system disorders, were lower in the ocrelizumab group". · This draft statement is not accurate. Only the incidence of serious infections and serious nervous system disorders, not overall incidence, were lower in the ocrelizumab group. [1]
32	4.3 Results – PPMS "The ORATORIO study was presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), but has not yet been published, which makes a full assessment of the trial difficult."	Remove this sentence. · The publication is enclosed for your review.
32	4.3 Results – PPMS	Add data for confirmed disease progression sustained for at least 24 weeks, which was significantly lower in the ocrelizumab group (HR 0.75, 95% CI 0.58-0.98, p=0.04).[3] · Earlier in the report (p.11), sustained disability progression for at least 24 weeks was preferred over 12 weeks.
32	4.3 Results – PPMS "As with rituximab, there was a significant reduction in the T2 lesion volume (p<0.001) and faster performance of the 25-foot walk (p=0.04)."	Remove the comparison of rituximab trial data in ocrelizumab section. · These were different trials and patient populations, and results should not be compared without appropriate qualifiers.
32	4.3 Results – PPMS "In summary, the trial demonstrated a significant 25-26% reduction in the rate of disability progression sustained at 12 and 24 weeks as well as a reduction in brain volume loss and in the rate of decline in walking speed."	Correct the reduction to 24-25% as there was a 24% reduction seen in confirmed disability progression sustained for ≥12 weeks and 25% reduction seen in confirmed disability progression sustained for ≥24 weeks in the ORATORIO trial. [3]
48	4.3 Results - Harms	Add the source of information presented for "D/C rates" (i.e. D/C

	Table 11 includes "D/C rates" and the type of DC is unknown (i.e. D/C due to AE, D/C due to any reason, etc.).	due to AE) · If discontinuation is due to AE, correct the "D/C rate" to 4% for ocrelizumab, which is consistent with the 3.5% and 4.1% reported in ocrelizumab-treated patients in the OPERA and ORATORIO trials, respectively).[1, 3]

Section 6: Comparative Value		
Page	**Excerpt from ICER draft report**	**Genentech Recommendation**
67	6.2 Cost-Effectiveness Model: Methods In Table 20, the equations for direct and indirect costs do not match the values of the annual direct and indirect costs.	Correct the equations to match the costs presented in Table 20.
81	6.5 Summary and Comment "Though some DMTs are more often used for later lines of therapy, none of their indications exclude first-line use, and there is no single treatment pattern for later lines of therapy."	Remove the incorrect statement "none of their indications exclude first-line use". · In the indication statements for daclizumab and alemtuzumab, the prescribing information states: Because of its safety profile, the use should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.[17, 18]

Appendices		
Page	**Excerpt from ICER draft report**	**Genentech Recommendation**
112, 116, 119, 123	Appendix C – Tables C1, C2, C3 and C4 Reference listed as Hauser 2015[58] for OPERA I and OPERA II trials.	Correct to Hauser 2016. · Please refer to the enclosed publication (Hauser, et al. 2016) for most updated reference for OPERA I and OPERA II trials.[1]
112, 116, 123, 127, 131	Appendix C – Tables C1, C2, C4, C5 and C6 Rituximab dose listed as 1000 mg IV.	Correct to Rituximab 2000 mg IV · In the HERMES study, patients received 1000 mg of intravenous (IV) rituximab on days 1 and 15 totaling 2000 mg IV rituximab in a single course.[8]
112	Appendix C – Table C1 Follow-up for OPERA I and OPERA II trials is listed as 12 months.	Correct follow-up to 22 months.[1]
116	Appendix C – Table C2 The source of the baseline demographic numbers in the table is unclear.	Add where baseline demographic data is sourced from in Table C2, i.e. intervention arm, both arms, averaged from each trial arm?
119	Appendix C – Table C3 For the quality assessment of OPERA I and OPERA II randomized controlled trials, the "comparable groups" quality criterion is listed as "Unclear".	For the "Comparable Groups" quality criterion for OPERA I and OPERA II trials, correct from "Unclear" to "Yes". · Please refer to Table 1 in the enclosed publication to see that baseline demographics and disease characteristics were similar between treatment groups and between studies.[1]
123	Appendix C – Table C4 For OPERA I, the ARR is reported as 0.155 for the ocrelizumab group and 0.290 for the interferon (IFN) beta-1a	Correct to 0.16 for the ocrelizumab group and 0.29 for the IFN beta-1a group.[1]

	group.	
123	Appendix C – Table C4 For OPERA I and OPERA II, the 95% CI for ARR is listed as "NR".	Change to include 95% confidence intervals for ARR as follows:[1] · OPERA I: 0.12-0.20 for the ocrelizumab group and 0.24-0.36 for the IFN beta-1a group. · OPERA II: 0.12-0.20 for the ocrelizumab group and 0.23-0.36 for the IFN beta-1a group.
123	Appendix C – Table C4 For OPERA I, the number of relapses listed for the IFN beta-1a arm is 223.	Correct to 221 per previous Genentech submission to ICER dated September 16, 2016.
150	Appendix E - Table E1 For ocrelizumab, administration costs are listed incorrectly.	Correct infusion costs for ocrelizumab: For RRMS, correct Year 1 infusion costs to $363.87 (2*($69.82+$18.98*2)+1.17*($69.82+$18.98*3)) and Subsequent Years to $275.07 (2.17*($69.82+$18.98*3). For PPMS, correct Year 1 and subsequent years infusion costs to $468.84 (4.35*($69.82+$18.98*2). Per 2016 CMS Physician Fee Schedule for CPT code 96365 (intravenous infusion, for therapy, initial, up to one hour) is $69.82 per one-hour infusion. CPT code 96366 (intravenous infusion, for therapy, each additional hour), which can be applied for each additional hour, is $18.98.[19]
158	Appendix E - Table E9 The "Initial RRMS EDSS State" column lists states 0 through 8.	Correct to include EDSS states 1 to > 9, not 0 to >8.[20] Please also check it is correctly input into the cost-effective analysis.
165	Appendix E - Table E11	Add a legend of qualifier to include the definition of the dark blue

It is unclear what the light and blue bars refer to.	and light blue bars in Table E11 and double check numbers. ● We assumed that dark blue refers to ICER's cost per QALY when the input parameter is low and the light blue bar refers to ICER's cost per QALY when the input parameter is at the high value. ● If this is the case, it can explain that when the annual cost for ocrelizumab is decreased, the ICER value would decrease. However, it does not explain the increase in ICER value when the relative risk of progression of ocrelizumab is decreased.

Table 1. Utilization of Off-label DMTs in Patients with PPMS (Adelphi Multiple Sclerosis DSP V)

Treatment Name	Percentage of PPMS patients (n=215)
Avonex	6%
Betaseron	7%
Extavia	0%
Rebif	2%
Copaxone 20mg	4%
Copaxone 40mg	5%
Glatopa	0%
Plegridy	0%
Aubagio	4%
Gilenya	5%
Tysabri	7%
Tecfidera	7%
Lemtrada	1%
Novantrone	1%
Other	6%
No drug treatment	47%

References:

1. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med 2016. DOI: 10.1056/NEJMoa1601277. Epub Ahead of Print. http://www.nejm.org/doi/full/10.1056/NEJMoa1601277.
2. Genentech, Data on file, December 2016.
3. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2016. DOI: 10.1056/NEJMoa1606468. Epub Ahead of Print. http://www.nejm.org/doi/full/10.1056/NEJMoa1606468?query=featured_home.
4. Adelphi Multiple Sclerosis DSP V (Q1 2016), Data on file, 2016.
5. Salter A, Thomas N, Cutter G, et al. The Profile of a Contemporary Cohort of Participants with Primary Progressive Multiple Sclerosis in the NARCOMS Registry. Presented at the 2016 Annual Meeting of the Consortium of Multiple Sclerosis Centers in National Harbor, MD, USA. CMSC oral presentation CC01. Available at http://www.mscare.org/.
6. Inusah S, Sormani Mp, Cofield SS, et al. Assessing changes in relapse rates in multiple sclerosis. Mult Scler. 2010 Dec;16(12):1414-21. https://www.ncbi.nlm.nih.gov/pubmed/20810517.
7. Bar-Or A, Calabresi P, Arnold D, et al. Rituximab in Relapsing-Remitting Multiple Sclerosis: A 72-Week, Open-Label, Phase I Trial. Ann Neurol 2008;63:395– 400.
8. Hauser SL, Waubant E, Arnold DL, et al. B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis. N Engl J Med 2008; 358:676-688. https://www.ncbi.nlm.nih.gov/pubmed/18272891.
9. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Annals of neurology.* 2009;66(4):460-471. https://www.ncbi.nlm.nih.gov/pubmed/19847908.
10. Miller DH, Leary SM. Primary-progressive multiple sclerosis. Lancet Neurol 2007; 6: 903-12. https://www.ncbi.nlm.nih.gov/pubmed/17884680.
11. Hoffmann-La Roche. A Study of Ocrelizumab in Participants With Relapsing Remitting Multiple Sclerosis (RRMS) Who Have Had a Suboptimal Response to an Adequate Course of Disease-Modifying Treatment (DMT). Available at https://clinicaltrials.gov/ct2/show/NCT02637856. Accessed on December 8, 2016
12. Hoffmann-La Roche. A Study of Ocrelizumab in Participants With Relapsing Remitting Multiple Sclerosis (RRMS) Who Have Had a Suboptimal Response to an Adequate Course of Disease-Modifying Treatment (DMT). Available at https://clinicaltrials.gov/ct2/show/study/NCT02861014. Accessed on December 8, 2016.
13. Hoffmann-La Roche. A Study to Evaluate the Effects of Ocrelizumab on Immune Responses In Participants With Relapsing Forms of Multiple Sclerosis. Available at https://clinicaltrials.gov/ct2/show/NCT02545868. Accessed on December 8, 2016
14. Hoffmann-La Roche. Study to Explore the Mechanism of Action of Ocrelizumab and B-Cell Biology in Participants With Relapsing Multiple Sclerosis (RMS). Available at https://clinicaltrials.gov/ct2/show/NCT02688985. Accessed on December 8, 2016
15. Hoffmann-La Roche. A Study of the Efficacy and Safety of Ocrelizumab in Patients With Relapsing-Remitting Multiple Sclerosis. Available at https://clinicaltrials.gov/ct2/show/NCT00676715. Accessed December 8, 2016.
16. De Seze J, Montalban X, McDougall F, et al. Patient-reported outcomes in the Phase III double-blind, placebo-controlled ORATORIO study of ocrelizumab in primary progressive multiple sclerosis. Presented at the 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis in London, United Kingdom; September 14–17, 2016. ECTRIMS Poster #P1279.
17. Zibryta [prescribing information]. Biogen Inc.; North Chicago, IL. 2016.
18. Lemtrada [prescribing information]. Genzyme Corporation; Cambridge, MA. 2014.
19. 2016 CMS physician fee schedule. https://www.cms.gov/apps/physician-fee-schedule/. Accessed August 1, 2016.
20. Mauskopf J, Fay M, Iyer R, Sarda S, Livingston T. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. *J Med Econ.* 2016;19(4):432-442.

NOVARTIS

Novartis appreciates the opportunity to provide feedback to ICER on the draft evidence report on disease-modifying therapies (DMTs) for multiple sclerosis (MS). MS is a chronic, neurodegenerative disease that leads to significant physical disability (leading cause of non-traumatic disability in young adults), cognitive decline, and lower quality of life.[1]

Novartis is committed to helping people living with MS and offers three medicines—Gilenya® (fingolimod), Extavia® (interferon beta-1b), and Glatopa® (glatiramer acetate)—ranging from a once-daily oral therapy to a generic injectable therapy. Fingolimod was the first oral DMT approved in 2010 for the treatment of relapsing forms of multiple sclerosis (RMS) and is the only oral DMT proven to reduce relapse rates by more than half in a head-to-head trial against an active comparator. Fingolimod provides a convenient, once-a-day, high efficacy oral DMT option that slows disability progression, reduces the occurrence of relapses, and improves MRI outcomes.[2] As of October 2016, approximately 160,000 patients have received fingolimod worldwide, and there were approximately 368,000 years of patient experience in both clinical trials and post-marketing studies.[3] The vast body of clinical trial and real world evidence supports fingolimod's ability to provide long-term, sustained efficacy and long-term safety in addition to tolerability and patient satisfaction to MS patients.[4-10]

We have highlighted evidence on fingolimod that should be incorporated into the revised evidence report. In addition, we have provided key considerations for changes to the methodology.

1. **The MS patient experience should be the focus and driving force of this report**: The efforts with the patient survey are a step in the right direction; however, these findings were not incorporated into main components of the report. ICER should incorporate the full burden of MS from the patient perspective directly into the "Evidence Rating Matrix" and cost-effectiveness model methodology.

2. **Incorporation of fingolimod's robust long-term data**: The robustness of the evidence on fingolimod, which meets ICER's criteria on "certainty" and "magnitude," warrants an improved "Evidence Rating Matrix" grade of an "**A**" versus best supportive care and a "**B**" or higher versus interferons or glatiramer acetate. **Fingolimod has:**
   a) Higher quality and more "certain" data as the only oral DMT with a positive head-to-head data against an active comparator (TRANSFORMS trial) and one of only three trials receiving the highest quality evaluation by ICER (FREEDOMS trial)[2,5-7]
   b) Long-term and consistent data on efficacy over 4.5 years and safety over 7 years[4,10,11]
   c) Extensive real-world and Phase IV evidence on comparative effectiveness, adherence, and patient satisfaction.[8,9,11]

3. **Consistency with approved indications**: Alemtuzumab and daclizumab's FDA approved indications are after "inadequate response to two or more drugs";[12,13] however, ICER incorrectly interprets line of therapy in the draft evidence report's comparative clinical effectiveness summary and cost-effectiveness model. Misrepresentation of DMT risk profiles and approved indications may jeopardize appropriate treatment benefit/risk assessments for MS patients.

4. **Methodological concerns and need for additional transparency**: ICER's report should incorporate the timing of loss of exclusivity (LOE) and availability of generic DMTs, which are important considerations especially for patients in regards to lower out-of-pocket costs. Further, to enhance the validity of the network meta-analysis (NMA) and cost-effectiveness models, additional information on assumptions and direct access to ICER's models are needed.

1. The MS patient experience should be the focus and driving force of this report.

The patient perspective should directly inform the main evaluations of the DMTs.
The patient survey results did not directly inform the decision-making around the draft evidence report's main sections on comparative clinical effectiveness, cost-effectiveness, or budget impact. We recommend that ICER include all patient-centric value components in the relevant models; failing to do so may underestimate DMTs' treatment benefit. More broadly, information on patient-reported outcomes (PRO)—available from well-controlled Phase IV data among other sources—should be considered in the report and model. Specifically, in the PREFERMS study, fingolimod patients had higher retention rates (81.3%) compared to injectable DMTs (29.2%) as well as improved treatment satisfaction.[9] In the EPOC study, patients who were on injectable DMTs switching to fingolimod versus staying on an injectable DMT had larger improvements in patient satisfaction as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM) as well as PROs on fatigue and depression.[8]

ICER's care value model should apply a societal perspective to measure DMTs full value.
ICER's scoping document included a broad list of clinical outcomes to be considered, but the draft evidence report included few outcomes in its cost-effectiveness ("care value") model. Although incorporating work productivity and other indirect costs in scenario analyses is a step in the right direction, failing to measure these components in the baseline model biases the baseline estimates towards lower cost-effectiveness. Furthermore, ICER should include caregiver time cost and disutility into the cost-effectiveness model, as has previously been done by National Institute for Health and Care Excellence (NICE).[14-17] The burden of RMS on patients and caregivers is large;[18-35] in one study, 47.1% of caregivers provided more than 20 hours of care per week. Further, ICER's approach fails to account for other key components of value including, but not limited to: (1) patient satisfaction, (2) functional status, and (3) societal value of innovation (e.g. "insurance value" ascribed to treatment from the perspective of individuals without MS).[32,36,37]

2. Incorporation of fingolimod's robust long-term data: Based on ICER's criteria, fingolimod's "Evidence Rating Matrix" grades should be improved

a) Fingolimod has higher quality data, as the only oral DMT with a positive head-to-head trial (TRANSFORMS) against an active comparator. In addition, the pivotal FREEDOMS trial was one of only three trials receiving the highest quality evaluation by ICER.
Fingolimod has proven to provide early and sustained high efficacy across a variety of disease activity measures versus standard-of-care (i.e. only oral DMT with positive results in a head-to-head trial) and placebo. Fingolimod has consistently demonstrated superior efficacy in terms of relapses vs. standard-of-care and placebo (TRANSFORMS, FREEDOMS, FREEDOMS II) and disability compared with placebo (FREEDOMS). The TRANSFORMS pivotal and extension trial demonstrated fingolimod's superior efficacy versus intramuscular interferon beta-1a and consistent safety profile.[10] For patients taking 0.5 mg of fingolimod, annualized relapse rates (ARR) were 0.16 (0.12-0.21), compared to 0.33 (0.26-0.42) for interferon beta-1a.[7] The consistency of fingolimod's clinical benefit compared to intramuscular interferon beta-1a was also seen across several subgroups, including MS patients with highly active disease.[38] Based on ICER's criteria, the "certainty" of fingolimod's evidence should be "higher" than dimethyl fumarate and natalizumab, which do not have head-to-head trials showing superiority compared to interferons or glatiramer acetate. Furthermore, despite the fingolimod trial, FREEDOMS, receiving one of only three highest quality clinical trial assessment ratings ("good") out of 39

RRMS trials, fingolimod received a similar "Evidence Rating Matrix" grade as dimethyl fumarate, an oral DMT with only "poor" quality trials. Thus, based on the available evidence, fingolimod should receive a rating of "B" or higher grade versus interferons/glatiramer acetate and a rating of "A" versus best supportive care.

Indirect comparisons demonstrate that fingolimod patients had a higher likelihood of achieving the "No Evidence of Disease Activity" composite endpoints (NEDA-3, NEDA-4), compared to other oral DMTs.[39] Also, fingolimod has demonstrated a significant reduction in brain volume loss (BVL) by 32% to 35% in pivotal trials compared to intramuscular interferon beta-1a and placebo, respectively.[6,7,38,40] Although ICER acknowledges the importance of these outcomes to patients, they are not reflected in the net health benefit ratings.

Increased transparency on the value ICER's methodology places on clinical benefits versus risks in their Evidence Rating Matrix" is needed. Despite alemtuzumab and natalizumab's black box warnings, both treatments receive an "A" rating compared to best supportive care. Given these significant risks, their importance to patients, and their respective U.S. labels' third line indication, alemtuzumab and natalizumab's net health benefit grade should be lowered.[12,13]

b) Fingolimod has demonstrated a sustained long-term efficacy and safety profile.

The FREEDOMS extension study (4 years)[41] and TRANSFORMS extension study (4.5 years)[10] confirmed the effect of fingolimod therapy in maintaining a low rate of disease activity and sustained improved efficacy, with no new safety concerns. In the TRANSFORMS extension study, patients in the continuous-fingolimod cohort demonstrated significantly lower (35%) ARR compared with those in the IFN β-1a switch cohort (0.17 vs. 0.27, respectively) after 4.5 years, suggesting improved outcomes for earlier, continuous use of fingolimod.[10] In the FREEDOMS extension study, patients who were continuously on fingolimod had a 48% reduction in ARR, 27% to 31% reduced risk of disability progression measured, and significantly lower BVL versus placebo patients who switched to fingolimod. The LONGTERMS study, the pooled extension study of fingolimod's Phase II/III programs over 7 years, found that fingolimod patients in extension phases had fewer or similar serious adverse events compared to patients taking fingolimod for 1 or 2 years in the pivotal trials [incidence rate ratio = 0.73 (0.60-0.91)][4]; efficacy measured by ARR and EDSS pooled of the TRANSFORMS and FREEDOMS cohorts were consistently maintained at reduced levels over 7 years.

The "Harms of DMTs" table should accurately reflect the safety profile of fingolimod.

In the draft evidence report, ICER states that fingolimod requires a REM (Table 11 and the "Harms" section). However, the FDA recently determined that the communication plan in the Risk Evaluation and Mitigation Strategy (REMS) for Gilenya (fingolimod) is no longer needed to ensure that the benefits of the drug outweigh the risks.[42]

c) ICER should consider fingolimod's Phase IV comparative satisfaction data and real world effectiveness in evaluations of comparative clinical effectiveness.

The word "effectiveness" in "comparative clinical effectiveness" implies that data beyond clinical trials were incorporated in the report. However, the net health benefit ratings do not currently consider real-world data or Phase IV studies, which are important to all stakeholders. As mentioned previously, fingolimod's retention, patient satisfaction, and other PROs were measured in the Phase IV studies, PREFERMS and EPOC. Evidence from the international MSBase registry indicates that patients switching to fingolimod were associated with a significant reduction (51%) in the rate of first relapse and significant slowing of disability progression, similar to natalizumab, compared to those switching to an interferon beta,

3

glatiramer acetate, teriflunomide or dimethyl fumarate.[43] In the prospective, non-interventional study PANGAEA, patients continuing fingolimod from trials had sustained reduction of ARR and stable EDSS over 4 years with 62.5% to 74.5% of patients with no clinical disease activity in any given year.[44] Additional comparative effectiveness studies have shown similar results on relapse prevention.[45] Several real-world studies based on data from national claims databases,[46-48] MS centers,[49] and international registries[50] demonstrated that patients taking fingolimod have high adherence and persistence rates, which are consistent with findings in the Phase IV PREFERMS study. Specifically, an MSBase Registry study[50] and MS Center[49] study have demonstrated that patients using fingolimod were significantly less likely to discontinue treatment in addition to having a trend towards better clinical outcomes (i.e. relapses) relative to dimethyl fumarate (as well as teriflunomide and injectable DMTs[50]). Finally, a cross-sectional PRO study found that patients taking fingolimod reported higher scores compared to dimethyl fumarate on satisfaction and tolerability.[11]

3. Consistency with approved indications: ICER should clearly state approved line-of-therapy indications and model therapy use only for indicated populations

ICER should apply care value modeling based on a treatment's indicated patient population. ICER incorrectly states that there is a "lack of conclusive FDA labels" to be able to compare first-line agents to later lines. Each DMT's FDA indication, however, is clear. Fingolimod is approved as a first-line RMS agent,[51] while alemtuzumab and daclizumab are indicated for use after "inadequate response to two or more drugs" "because of [their] safety profile."[12,13] ICER's methodology should reflect these indications. In the cost-effectiveness model, ICER states that "after discontinuation from second-line therapy, patients transitioned to best supportive care," implying that alemtuzumab and daclizumab are modeled for non-indicated, second line use. Further, FDA-approved lines of therapy for all DMTs should be included in Table 1. Failing to do so may jeopardize appropriate treatment benefit/risk assessments for MS patients.

ICER should remove voting question #4 comparing daclizumab to dimethyl fumarate or fingolimod and should revise question #1 comparing dimethyl fumarate to fingolimod. The direct comparison of two treatments with different indications is problematic. Since daclizumab is only indicated for third-line therapy, any comparisons should be made for similar, third-line therapies as per labeling. In addition, question #1 is phrased in a biased manner as it does not allow for the voters preferring fingolimod to voice their view. ICER should instead ask which DMT has the higher net health benefit, as this would allow voters to select among (i) fingolimod, (ii) dimethyl fumarate, or (iii) that the evidence is insufficient.

ICER should exclude rituximab as it is not indicated for the treatment of RMS. A Cochrane Review's NMA concluded that: "There is not sufficient evidence to support the use of rituximab as a [DMT] for RRMS."[52] The only comparative trial of rituximab included in the NMA was cited as high risk of bias due to high attrition.[53] This study was not sufficiently powered to detect changes in important endpoints such as relapses, BVL, and safety. Off-label use of rituximab may have public safety consequences, particularly in light of boxed warnings and reported data on serious adverse events for on-label indications.[7]

4. Methodological concerns and need for additional transparency

The cost-effectiveness model should incorporate price decreases after loss of exclusivity. When modeling cost-effectiveness, ICER should account for future drug price adjustments to reflect the effect of loss of exclusivity (LOE). Historically, among recent generic entrants,

ⵁ NOVARTIS

generic oral medications had 74% lower prices than the pre-expiry brand prices within 8 months of becoming available[54] and 93% adoption of the generic (vs. brand) within a year;[55] these decreases are much larger than those for generic biologic (i.e. large molecules) medications, which have greater manufacturing complexities and fewer competitors.[56,57] Fingolimod is an oral DMT for which the compound patent expires in the near future, which may lead to LOE during the time horizon used in ICER's cost-effectiveness model. Incorporating the availability of lower cost generic versions within the model's time horizon better reflects the true cost-effectiveness calculations as a drug nears its LOE and is consistent with good practice recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[58,59]

ICER's baseline analysis should separately analyze trials based on whether disability progression was measured over a 12-week or 24-week time period using high quality evidence.
The evidence from trials that confirmed disability progression at 12-weeks or 24-weeks is not comparable. A 24-week disability duration leads to fewer acute incidences of improvement or worsening because patients in 24-week trials need to show change in disability for a longer duration of time compared to 12-week trials. This approach reduces the occurrence of smaller, temporary changes being reported (i.e., fewer 'false-positives').[60-62] Thus, using 12-week and 24-week results in a single NMA results in an inappropriate comparison. Further, the disability endpoint used leads to large differences in care value estimates. In the baseline approach, fingolimod's incremental cost-effectiveness was $576,325 per QALY compared to glatiramer acetate, whereas in the sensitivity analysis incorporating only trials with 12-week disability progression, the cost per QALY was $119,764 (i.e. below the ICER threshold of $150,000 per QALY). This large difference in care value suggests that trials using 12 and 24-week disability progression measures may not be comparable.

NMA should measure effectiveness for the target population and test all model assumptions.
There has not been an evaluation whether differences in follow-up affect the ARR estimates. With the approach taken by ICER it is implicitly assumed that relapse follows an exponential distribution with a constant underlying rate. The question is whether this is true and if not, whether the within-trial rate ratios are different at different follow-up times. If this is the case, then differences in follow-up between trials might bias NMA results.

Despite adjusting for between-trial differences, it is not clear whether treatment effect estimates are relevant for the target populations of interest.
A meta-regression of all trials adjusting for proportion of experienced patients to obtain results for treatment-naïve as well as treatment-experienced patients would be a relevant sensitivity analysis, especially with NMA results used in the cost effectiveness model where all patients are treatment-naïve to begin with and switch to a second DMT after failure.

ICER's approach for measuring drug prices and discounts should be transparent.
Discount and rebate information obtained from SSR Health are not shared in the current report. Details of the methodology used in these calculations should be disclosed.

ICER should provide clarity on whether treatment efficacy in terms of delaying disability progression has been included in the cost-effectiveness model for EDSS transitions in SPMS.
It is currently unclear as to whether the natural history transitions between EDSS states in SPMS are adjusted for treatment efficacy. More clarity is required to describe the modeling approach.

Marcia Kayath
VP and Head, US Clinical Development & Medical Affairs

Amy Rudolph
VP and Head, Early Development and HE&OR

References

1. Multiple Sclerosis International Federation. Atlas of MS 2013: Mapping Multiple Sclerosis Around the World: Multiple Sclerosis International Federation; 2013.
2. Food and Drug Administration. HIGHLIGHTS OF PRESCRIBING INFORMATION Gilenya2016.
3. Novartis Pharmaceuticals. Investor Relations Report Q3 20162016 October 2016.
4. Cohen J, Von Rosenstiel P, Gottschalk R, Pradhan A, Zhang Y, Kappos L. Long-term Safety of Fingolimod: An Interim Analysis of the LONGTERMS Cohort (S4. 006). Neurology 2015;84:S4. 006.
5. Calabresi PA, Radue E-W, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Neurology 2014;13:545-56.
6. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362:387-401.
7. Cohen JA, Barkhof F, Comi G, et al. TRANSFORMS study group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362:402-15;
8. Fox E, Edwards K, Burch G, et al. Outcomes of switching directly to oral fingolimod from injectable therapies: Results of the randomized, open-label, multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis. Multiple Sclerosis and Related Disorders;3:607-19.
9. Cree B, Wynn D, Cascione M, Meng X, Schofield L, Tenenbaum N. Key Results from PREFERMS: Real-World Patient Retention and Outcomes on Fingolimod versus Platform Injectable Disease-Modifying Therapies in Early Relapsing-Remitting Multiple Sclerosis (P3. 115). Neurology 2016;86:P3. 115.
10. Cohen JA, Khatri B, Barkhof F, et al. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. Journal of Neurology, Neurosurgery & Psychiatry 2016;87:468-75.
11. Wicks P, Rasouliyan L, Katic B, Nafees B, Flood E, Sasané R. The real-world patient experience of fingolimod and dimethyl fumarate for multiple sclerosis. BMC Research Notes 2016;9:434.
12. US Food and Drug Administration. HIGHLIGHTS OF PRESCRIBING INFORMATION Lemtrada: Food and Drug Administration,; 2014.
13. Food and Drug Administration. HIGHLIGHTS OF PRESCRIBING INFORMATION: Zinbryta: Department of Health and Human Services,; 2016.
14. National Institute for Clinical Excellence. Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis. London: NICE 2007.
15. National institute for Clinical Excellence. Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis. London: NICE 2012.
16. National institute for Clinical Excellence. Dimethyl fumarate for treating relapsing‑remitting multiple sclerosis. London: NICE 2014.
17. National institute for Clinical Excellence. Alemtuzumab for treating relapsing‑remitting multiple sclerosis. London: NICE 2014.
18. Pike J, Jones E, Rana J, Lee A, Iyer R. Differences In Work Productivity Activity Imparment In Rrms Patients Initiated on Oral Dmf or Platform Therapies In Europe and Us. Value Health 2015;18:A759.

19. Kobelt G, Berg J, Atherly D, Hadjimichael O. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. Neurology 2006;66:1696-702.
20. Parise H, Laliberte F, Lefebvre P, et al. Direct and indirect cost burden associated with multiple sclerosis relapses: excess costs of persons with MS and their spouse caregivers. J Neurol Sci 2013;330:71-7.
21. Kobelt G. Costs and quality of life for patients with multiple sclerosis in Belgium. Eur J Health Econ 2006;7 Suppl 2:S24-33.
22. Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life in multiple sclerosis in The Netherlands. Eur J Health Econ 2006;7 Suppl 2:S55-64.
23. Kobelt G, Berg J, Lindgren P, Battaglia M, Lucioni C, Uccelli A. Costs and quality of life of multiple sclerosis in Italy. Eur J Health Econ 2006;7 Suppl 2:S45-54.
24. Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life of multiple sclerosis in Germany. Eur J Health Econ 2006;7 Suppl 2:S34-44.
25. Kobelt G, Berg J, Lindgren P, Fredrikson S, Jonsson B. Costs and quality of life of patients with multiple sclerosis in Europe. J Neurol Neurosurg Psychiatry 2006;77:918-26.
26. Kobelt G, Berg J, Lindgren P, Gerfin A, Lutz J. Costs and quality of life of multiple sclerosis in Switzerland. Eur J Health Econ 2006;7 Suppl 2:S86-95.
27. Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life of multiple sclerosis in Spain. Eur J Health Econ 2006;7 Suppl 2:S65-74.
28. Kobelt G, Berg J, Lindgren P, Kerrigan J, Russell N, Nixon R. Costs and quality of life of multiple sclerosis in the United Kingdom. Eur J Health Econ 2006;7 Suppl 2:S96-104.
29. Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life of multiple sclerosis in Austria. Eur J Health Econ 2006;7 Suppl 2:S14-23.
30. Kobelt G, Kasteng F. Access to innovative treatments in multiple sclerosis in Europe. A report prepared for the European Federation of Pharmaceutical Industry Associations (EFPIA)2009.
31. Ivanova JI, Bergman RE, Birnbaum HG, Phillips AL, Stewart M, Meletiche DM. Impact of medication adherence to disease-modifying drugs on severe relapse, and direct and indirect costs among employees with multiple sclerosis in the US. J Med Econ 2012;15:601-9.
32. Gupta S, Goren A, Phillips AL, Stewart M. Self-reported burden among caregivers of patients with multiple sclerosis. Int J MS Care 2012;14:179-87.
33. McCrone P, Heslin M, Knapp M, Bull P, Thompson A. Multiple sclerosis in the UK: service use, costs, quality of life and disability. Pharmacoeconomics 2008;26:847-60.
34. Buchanan R, Huang C. Health-related quality of life among informal caregivers assisting people with multiple sclerosis. Disabil Rehabil 2011;33:113-21.
35. Buchanan RJ, Radin D, Huang C. Burden among male caregivers assisting people with multiple sclerosis. Gend Med 2010;7:637-46.
36. Shih T, Wakeford C, Meletiche D, et al. Reconsidering the economic value of multiple sclerosis therapies. The American journal of managed care 2016;22:e368.
37. Kister I, Bacon TE, Chamot E, et al. Natural history of multiple sclerosis symptoms. Int J MS Care 2013;15:146-58.
38. Cohen JA, Barkhof F, Comi G, et al. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. J Neurol 2013;260:2023-32.
39. Nixon R, Bergvall N, Tomic D, Sfikas N, Cutter G, Giovannoni G. No evidence of disease activity: indirect comparisons of oral therapies for the treatment of relapsing-remitting multiple sclerosis. Adv Ther 2014;31:1134-54.

40. Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13:545-56.

41. Kappos L, O'Connor P, Radue E-W, et al. Long-term effects of fingolimod in multiple sclerosis The randomized FREEDOMS extension trial. Neurology 2015;84:1582-91.

42. Food and Drug Administration. SUPPLEMENT APPROVAL RELEASE REMS REQUIREMENT Silver Spring, Maryland, USA: Department of Health and Human Services; 2016.

43. Comparative analysis of MS outcomes in natalizumab-treated patients using a novel three-way multinomial propensity score match. European Committee for Treatment and Research in Multiple Sclerosis, 2016. (Accessed November 29, 2016, at http://onlinelibrary.ectrims-congress.eu/ectrims/2016/32nd/145839/tim.spelman.comparative.analysis.of.ms.outcomes.in.natalizumab-treated.html?f=m2s440992.)

44. Ziemssen T, Albrecht H, Haas J, Klotz L, Lang M, Lassek C, Schmidt S, Tackenberg B, Cornelissen C. Development of former fingolimod study patients in a real world setting: results from the 4 year interim analysis of the non-interventional trial PANGAEA (P.1224). European Committee for Treatment and Research in Multiple Sclerosis 2016.

45. Bergvall N, Makin C, Lahoz R, et al. Relapse rates in patients with multiple sclerosis switching from interferon to fingolimod or glatiramer acetate: a US claims database study. PLoS One 2014;9:e88472.

46. Agashivala N, Wu N, Abouzaid S, et al. Compliance to fingolimod and other disease modifying treatments in multiple sclerosis patients, a retrospective cohort study. BMC neurology 2013;13:1.

47. Johnson K, Zhou H, Lin F, Ko J, Herrera V. Adherence and Persistence to Oral MS Disease Modifying Treatment in a Real-World Setting Journal of Managed Care & Specialty Pharmacy 2015;21.

48. Kantor D, Ko J, Antol D, et al. The Impact of Step Therapy on Oral Disease-Modifying Treatment Initiation Rates for Patients with Multiple Sclerosis. Journal of Managed Care & Specialty Pharmacy 2016;22.

49. Vollmer B, Nair K, Sillau S, Corboy J, Vollmer T, Alvarez E. Comparison of Fingolimod and Dimethyl Fumarate in the Treatment of Multiple Sclerosis: Two Year Experience (S24. 004). Neurology 2016;86:S24. 004.

50. Spelman T, Kalincik T, Trojano M, et al. Comparative analysis of MS outcomes in dimethyl fumarate-treated patients relative to propensity matched fingolimod, interferon, glatiramer acetate, or teriflunomide. European Committee for Treatment and Research in Multiple Sclerosis 2016.

51. Francis G, Collins W, Burtin P. Fingolimod (NDA 22-527) Briefing Document 2010.

52. National Insitute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. In: NHS, ed.: National Institute for Health and Care Excellence; 2013.

53. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. The New England journal of medicine 2008;358:676-88.

54. Price declines after branded medicines lose exclusivity in the U.S. 2016.

55. Grabowski H, Long G, Mortimer R, Boyo A. Updated trends in US brand-name and generic drug competition. Journal of medical economics 2016:1-9.

56. Ahlstrom A, King R, Brown R, Glaudemans J, Mendelson D. Modeling federal cost savings from follow-on biologics. Avalere, April 2007.

57. Grabowski HG, Ridley DB, Schulman KA. Entry and competition in generic biologics. Managerial and Decision Economics 2007;28:439-51.

58. Guertin JR, Mitchell D, Ali F, LeLorier J. Bias within economic evaluations - the impact of considering the future entry of lower-cost generics on currently estimated incremental cost-effectiveness ratios of a new drug. Clinicoecon Outcomes Res 2015;7:497-503.

59. Mycka JM, Dellamano R, Kolassa EM, et al. Good research practices for measuring drug costs in cost effectiveness analyses: an industry perspective: the ISPOR drug cost task force report—Part V. Value in Health 2010;13:25-7.

60. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis (EMA/CHMP/771815/2011, Rev. 2). London, UK: European Medicines Agency; 2015.

61. Cohen JA, Reingold SC, Polman CH, Wolinsky JS, International Advisory Committee on Clinical Trials in Multiple S. Disability outcome measures in multiple sclerosis clinical trials: current status and future prospects. Lancet Neurol 2012;11:467-76.

62. Rio J, Nos C, Tintore M, et al. Assessment of different treatment failure criteria in a cohort of relapsing-remitting multiple sclerosis patients treated with interferon beta: implications for clinical trials. Ann Neurol 2002;52:400-6.

Sanofi Genzyme welcomes the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on the effectiveness and value of disease-modifying therapies for Relapsing-Remitting Multiple Sclerosis (RRMS) and Primary-Progressive Multiple Sclerosis (PPMS). Multiple Sclerosis (MS) can be a crippling, heterogeneous disease that afflicts over 400,000 people in the U.S. and 2.3 million people worldwide (1, 2). The consequences for patients and their families can be physically and emotionally devastating. Due to the heterogeneity of the MS patient population, it is vitally important that treatment be determined based on individual patient needs, and thus patients must have access to all approved products. Sanofi Genzyme is committed to improving the lives of those affected by this disease.

Sanofi Genzyme is concerned about the application of ICER's methodology, the implementation of ICER's analysis and the characterization of some of the report's findings. Problems with each of these have led to misleading conclusions. Our critique revolves around several key points:

- The network meta-analysis (NMA) as applied to MS in this ICER report is based on some questionable assumptions. Among the concerns are inclusion of inappropriate studies and exclusion of appropriate studies. We are particularly concerned by the impact that heterogeneous patient populations, changes in diagnostic criteria over time and other significant differences between the trials conducted on the multiple MS therapies approved over the last three decades has on the analysis, which ICER has not accounted for. Additional concerns are related to pooling results from a variety of studies irrespective of differences in statistical power, pre-specified endpoints or length of follow up.

- NMA results have substantial uncertainty and limitations which should be highlighted in the report and its conclusions. The degree of consistency with other NMAs is overstated.

- Non-approved drugs in MS should not be included in this review as their benefit risk profile in MS has not been established and no label can therefore guide their evaluation.

- The methodology used to compute number needed to treat (NNT) is flawed and therefore results in misleading conclusions.

- ICER should change the criteria used to assess the quality of studies included in the report.

- Figure 5 is subjective and not driven by a quantitative analysis. Therefore, it should be removed from the final report.

- The report does not adequately address the issue of patient heterogeneity and differences in patient preferences and the many serious challenges faced by patients, which is important for recognizing the value to society of having all approved drugs available for patients.

Concerns Related to the Network Meta-Analysis (NMA)

All NMAs run the risk of oversimplification because they combine information from heterogeneous studies that involve different comparators. It is important to articulate the limitations of these syntheses and recognize the potentially high degree of uncertainty in conclusions. ICER's NMA is no exception.

An NMA tends to be valid only if the included studies are very similar to one another. If there are large variations between the included trials, broad generalizations of the effectiveness of interventions should not be made, as was done in this ICER report. Even in a conventional meta-analysis, errors or bias in an included study will result in biased conclusions. In an NMA, the problems with an errant or biased study are compounded because that study's biases will generally affect many comparisons (3-5).

Given the above consideration for general NMAs, the application of NMA in the MS disease area needs a very careful interpretation. Clinical studies in RRMS have shown very heterogeneous outcomes, including the placebo group rates.

As both the ICER clinical and cost effectiveness results are based on the NMA, limitations of these findings need to be prominently discussed and acknowledged.

- *Study Selection for Inclusion in NMA*
  - The inclusion or exclusion of individual studies has a significant impact on the outcomes of the analysis, and therefore trial selection must be based on critical evaluation. In some cases in the MS analysis, ICER has made incorrect decisions around study selection. It is essential to include the appropriate studies to obtain the most meaningful results.
  - An example of a study that should not have been included is the Bornstein, et al. study from 1987 (6). This study was a pilot trial conducted three decades ago and is the oldest study included in the NMA [report p.26; Tables C1-C3 Appendix]. Furthermore, the very small treatment arm (n=25) displayed different characteristics from the placebo group that exaggerate the observed magnitude of superiority of Cop 1 (glatiramer acetate [GA]). The result from this study is a significant outlier with a relative reduction in ARR almost 5 times greater than placebo -- a result never replicated. Finally, we would note the authors cautioned against drawing conclusions as it was a pilot study.
  - Another study that should not be included is TENERE. Unlike other studies included in the analysis, the TENERE study employed a unique composite primary endpoint of time to treatment failure.
  - An example of a study that was not included but should have been is the GATE study (7). GATE is a relevant Phase III study that studied three treatments: Copaxone, placebo and generic glatiramer acetate. This study meets all study selection criteria applied by ICER. It was published in the timeframe of other studies included (Dec. 2015 issue of JAMA Neurology).

- *Concerns about Including Results from Non-comparable Studies*
  - Another general concern with the conduct of the ICER NMA was the decision to include results and endpoints/outcomes from studies that are not similar. NMAs lose their

validity if results are included from studies that are dissimilar in terms of patient populations or other study characteristics.

- o This is clearly evident in calculations of disability progression in the different studies, as ICER combines results from trials which included different pre-specified disability progression endpoints (e.g. disability progression at 12 or 24 weeks). For individual therapies, studies have shown that when both 12 and 24 weeks outcomes are measured, the outcomes are typically different. Combining such results in one analysis, leads to misleading and invalid conclusions. For example, teriflunomide (both 7mg and 14mg) is no longer 'dominated' when compared with generic glatiramer acetate (GA) on either the cost per additional QALY or cost per additional life year criteria when only studies that consistently measure disability progression at 12 weeks are included.

- *Insufficient Discussion of Sensitivity and Uncertainty of Results*
  - o Given the known limitations of NMAs, ICER should include in the body of the report more thorough discussion of the sensitivity analyses currently only included in the appendix. For example, both dosage forms of teriflunomide show a credible range of cost effectiveness that is not dominated by GA 20mg (Glatopa). This finding should be in the body of the report but currently does not appear until appendix table E16 on page 175.

- *Misleading conclusions from ICER NMA analysis*
  - o Indirect comparisons can lead to wrong conclusions about the efficacy of a given product. For example, in direct studies versus placebo, GA 20 mg showed no statistically significant difference and little numerical difference (Johnson 1995 and CONFIRM) on slowing disability progression (8, 9). Despite the lack of positive findings on slowing disability progression as described above, in this NMA GA 20 mg is reported to be significantly superior to placebo on this endpoint. Therefore, GA 20mg should not be included in the relative risk reduction analysis for EDSS progression.

- *Consistency with Other NMAs*
  - o ICER's results for annualized relapse rate (ARR) and disability progression are not consistent with previous MS NMAs. There are clear variations in NMA results reported by Cochrane, CADTH, Tolley, and Fogarty in Tables 7 and 10 compared to ICER, and not all numbers in the table represent the same basis of measurement. The fact that each of these NMAs has different results highlights the limitations of MS NMAs.

- *Comments on Non-Approved Products*
  - o Rituximab should not be included in this report. There are no well-controlled Phase III studies that establish the safety and efficacy of rituximab in MS. As a result, there are no rigorous data to establish a benefit risk profile. Additionally, there is no label for its use in MS to guide data inclusion in this evidence evaluation.

- o For ocrelizumab, it must be noted the current results depend on assumptions ICER made about the clinical profile of the product, monitoring requirements, price etc., limiting the accuracy of the inputs. Therefore, some of the current results are not valid. If ocrelizumab is approved, analyses will need to be updated based on labeling and price.

Problems with Number Needed to Treat (NNT) Analysis

- o The methodology used to calculate the NNT to prevent one relapse or to prevent disability progression in the ICER analysis is flawed. ICER's calculation of NNT to prevent one relapse is based on a "background (i.e., placebo) relapse rate of 0.5622 relapses per year" and NNT to prevent one patient from experiencing disability progression is based on "a background (i.e., placebo) risk for disability progression of 0.176". For appropriate analysis, absolute risk reduction must be calculated based on drug and placebo (or comparator) results within a given study and its inverse (1/absolute risk reduction) must be used to calculate NNT for relapse rate. This is required because MS studies do not have a common set of baseline parameters (e.g. region, age, race, year of study conduct) or a common set of disease and prior treatment characteristics (e.g. disease duration, pre-baseline relapse activity, baseline EDSS, MRI activity, prior DMTs use status), and include unique study populations. Thus the results of the placebo arm vary greatly between studies (e.g. range of placebo annualized relapse rates in the ICER report range from 0.33 to 1.35 [source: Table C4 of report]. The same rationale holds for the NNTs derived for the disability progression endpoint.

- o When NNTs are calculated for each individual study correctly, they can then be used to compare across trials when head to head studies are not available.

Rating of Quality of Studies

- o ICER should reassess how they rated the quality of the clinical studies in the report. Specifically, classifying studies with 20% (or more) loss to follow-up as poor quality (Page 27 and Table C3) is not a sound approach. By using this criterion, several well-designed, well-conducted, high quality, long term double blinded Phase III studies have been rated as poor quality, while placebo-controlled, shorter duration Phase II studies with non-clinical primary endpoints are rated as fair-to-good quality. There is higher probability of patient drop out in longer duration studies (typically Phase III studies) compared to shorter duration, placebo-controlled Phase II studies. In addition, some Phase III studies have protocol-driven mandatory study discontinuation rules that lead to patient withdrawal, independent of patient or physician decision to do so. This results in higher frequency of drop outs. Thus the use of 20% loss to follow-up criteria results in incorrect rating of study quality. Furthermore, the Code of Federal Regulations states that an adequate and well-controlled study consists of: 1) A clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results; 2) A design that permits a valid comparison with a control to provide a quantitative assessment of drug effect; 3) The study drug being compared with an inactive preparation designed to resemble the test drug as far as possible; and 4) An analysis of the results of the study which is adequate to assess the

effects of the drug (21 C.F.R. § 314.126 (2016). The fulfillment of the above criteria has led to approval of DMTs by the FDA yet ICER's classification approach categorizes several of these studies as poor quality.
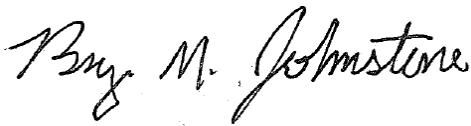
Figure 5 is Not Data-Driven
- o   Figure 5, a depiction of safety and effectiveness of different products, should be removed from the report. The size and location of the elements in the graph are subjective and not based on quantitative analysis and thus this figure has no place in a data-driven report.

Limitations Due to the Lack of Inclusion of Other Measures of Value
- o   These results would be more meaningful for patients and health care providers in making treatment decisions if they included attributes of a drug that have not been captured such as route of administration and aspects of tolerability and dosing. For example, ICER does not adequately address the serious challenges patients may experience with alternative routes of administration and accompanying side effects, and the resulting impacts on tolerability and adherence. Additionally, indirect costs (e.g. work absences, caregiver time, lost income, early retirement etc.) need to be considered as they often contribute significantly to total costs. For example, in the ICER analysis, indirect costs are more than double the size of direct costs in MS.

We thank ICER for the opportunity to comment on their draft report on therapies for the treatment of MS.

Bryan M. Johnstone, Ph.D.
Head, Evidence Synthesis, PROs, and Communications
Global Health Economics and Outcomes Research
Sanofi Genzyme

REFERENCES

1.   National Multiple Sclerosis Society. Multiple Sclerosis FAQs 2016 [Available from: http://www.nationalmssociety.org/What-is-MS/MS-FAQ-s - question-How-many-people-have-MS.
2.   Tullman MJ. Overview of the epidemiology, diagnosis, and disease progression associated with multiple sclerosis. Am J Manag Care. 2013;19(2 Suppl):S15-20.
3.   Li T, Puhan MA, Vedula SS, Singh S, Dickersin K, Ad Hoc Network Meta-analysis Methods Meeting Working G. Network meta-analysis-highly attractive but more methodological research is needed. BMC Med. 2011;9:79.
4.   Roehm E. Improving Medical Statistics: Limitations of Meta-Analyses 2005 [Available from: http://www.improvingmedicalstatistics.com/Limitations of Meta-analysis1.htm.
5.   Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ. 2009;338:b1147.
6.   Bornstein MB, Miller A, Slagle S, Weitzman M, Crystal H, Drexler E, et al. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. N Engl J Med. 1987;317(7):408-14.
7.   Cohen J, Belova A, Selmaj K, Wolf C, Sormani MP, Oberye J, et al. Equivalence of Generic Glatiramer Acetate in Multiple Sclerosis: A Randomized Clinical Trial. JAMA Neurol. 2015;72(12):1433-41.
8.   Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367(12):1087-97.
9.   Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45(7):1268-76.

Teva Pharmaceuticals   December 21, 2016
41 Moores Road ‖ Frazer, PA 19355

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review

RE: Draft Evidence Report Open for Public Comment (dated November 22, 2016) for Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value

Dear Dr. Pearson,

Thank you for the opportunity to review and comment on the draft evidence report. Teva has reviewed the report and respectfully provides our comments specifically pertaining to 1) use of Relative Risk (RR) of Disability Progression estimate for Copaxone® 40 mg TIW, 2) the assumptions related to medication discontinuation rates; and 3) reported differences between Copaxone® and Glatopa® to consider in the analysis approach.

Relative Risk of Disability Progression Estimate for Copaxone® 40 mg TIW Used in the Analysis

As ICER has noted on page 40 of the draft evidence report, "*It is unlikely that glatiramer acetate 40 mg increases disability progression.*" We fully concur with ICER on this item. However, we also note with concern that the ICER analyses nevertheless apply the RR estimate of 1.18 for Copaxone® 40 mg TIW (implying that the treatment increases disability progression) as the base case, which would likely lead to invalid effectiveness and value conclusions relating to Copaxone® 40 mg TIW. **We suggest to ICER to use an assumption in the cost-effectiveness model that the clinical effectiveness in slowing disability progression for Copaxone® 40 mg TIW is equivalent to that estimated for Copaxone® 20 mg QD (RR=0.70; 95% CI 0.54-0.93) and provide our rationale below.**

The application of the statistically non-significant disability RR of 1.18 (95% CI 0.67-1.97; p=0.57) for Copaxone® 40 mg TIW in the ICER model is based upon data from the one-year randomized placebo-controlled GALA study (Khan 2013) which does not reflect the underlying true clinical benefit of Copaxone® 40 mg TIW in slowing disability progression for patients with RRMS and, moreover, lacks face validity for the following reasons:

1. One year of observation is insufficient (too brief) to observe or infer a robust assessment of disability progression, thus this outcome must be utilized and interpreted with extreme

caution. A minimum requirement to obtain two consecutive measurements of EDSS a minimum of 6 months apart to establish Confirmed Disability Progression (CDP) is suggested by the European Medicines Agency (EMA 2015). The necessity for confirmation of the EDSS change of 1 or more points, at consecutive measurement intervals 12 or 24 weeks apart, to be considered as CDP allows only a few events of disability progression to occur and be confirmed during a one-year study, as has been observed in GALA (Table 1, Khan 2013).

Table 1. GALA (MS-GA-301) - Placebo Controlled (PC) Phase – Post Hoc Analysis. EDSS Data Distribution of the Number of Subjects with 3 Month Confirmed EDSS Progression during the PC Phase

GALA (MS-GA-301)	Placebo (N=461)		Glatiramer Acetate 40 mg TIW (N=943)	
	N	%	N	%
All	461	100.0	943	100.0
No progression	444	96.3	901	95.5
Confirmed EDSS progression	17	3.7	42	4.5

International guidance suggests that longer-term assessment is required to effectively evaluate treatment effects with respect to disability owing to the slow natural progression in RRMS (EMA 2015). For example, the European Medicines Agency states that "…*For a distinct claim on disability large-scale long-term parallel group trials will be required to establish clinically relevant treatment effects on disease progression. Study duration will depend on the population studied, and should be sufficient to show a reliable and relevant effect on disability. Such a study may need to last ~3 years*" (EMA 2015). Based on this guidance, it can be reasonably inferred that a one-year assessment of disability progression is scientifically inadequate and lacks robustness.

It is suggested that, for a valid claim on disability, large-scale long-term parallel group trials are required for a new DMT to establish clinically relevant treatment effects on CDP (EMA 2015).

2. The development program for Copaxone® 40 mg TIW included a single one-year phase 3 placebo controlled study to assess the safety and efficacy of the new dosing regimen of the same active drug substance as Copaxone® 20 mg QD but with less frequent injections (Khan 2013). The study was designed to detect a difference between Copaxone® 40 mg TIW vs placebo in the primary endpoint, the annualized relapse rate (ARR). It was not designed to detect a significant effect on the exploratory endpoint of CDP. In fact the

power to detect a significant difference in CDP in GALA would be about 7%, compared to the usual power of 80-90% for a primary endpoint in a clinical trial. Therefore, the disability progression RR generated compared to placebo is based only upon a limited number of events occurring (Table 1), further highlighting the robustness concerns of this one-year estimate.

3. The two-year open-label extension phase of the one-year GALA controlled clinical trial provides an estimate of disability progression for Copaxone® 40 mg TIW over three years ("Early Start" group) relative to one year of placebo plus two years of Copaxone® 40 mg TIW ("Delayed Start" group). Indeed, in the GALA three-year open-label extension, there was a trend towards a reduction in disability with Copaxone® 40 mg TIW (early start vs delayed start) although this was not statistically significant [hazard ratio (HR) = 0.76, 95% CI 0.55-1.04, p=0.09)] (Khan 2016). The HR and the corresponding disability RR for Copaxone® 40 mg TIW from the GALA extension study represent a conservative estimate of the actual benefits of Copaxone® 40 mg TIW in reducing disability progression as the delayed start arm data include treatment with placebo and two years of Copaxone® treatment as well. These data indicate that the one-year estimate used by ICER to estimate the Comparative Clinical Effectiveness of Copaxone® 40 mg TIW is inconsistent with the observed disability progression over longer follow-up (Khan 2016) and is therefore misleading and inappropriate.

To avoid a glaring analysis weakness related to Copaxone® 40 mg TIW and based on available data on clinical efficacy (highlighted below) we suggest ICER uses the assumption in the cost-effectiveness model that the disability progression RR for Copaxone® 40 mg TIW is equivalent to that estimated for Copaxone® 20 mg QD (RR=0.70; 95% CI 0.54- 0.93). Likewise, a prediction model and meta-analyses comparing Copaxone® 20 mg QD to Copaxone® 40 mg TIW results in similar clinical and MRI outcomes (Cutter 2014a; Cutter 2014b). The European Union (EU) regulatory agencies considered this comparison across study data, supporting the similarity of effects of Copaxone® 20 mg QD and Copaxone® 40 mg TIW on relapse rates, when approving Copaxone® 40 mg TIW in the EU, as summarized on pages 16-17 of the Copaxone® 40 mg TIW Public Assessment Report (MHRA 2015). Sormani et al. (2010) demonstrated a strong correlation of the effect of DMTs on relapses and CDP, and due to the similarity of effect on relapses between Copaxone® 20 mg QD and Copaxone® 40 mg TIW, it is a reasonable assumption, in the absence of an appropriate trial examining the effect of Copaxone® 40 TIW on disability, that Copaxone® 20 mg QD and Copaxone® 40 mg TIW have similar effects on CDP.

To provide further validity to this assumption that Copaxone® 20 mg QD and Copaxone® 40 mg TIW will have a similar effect on the CDP, using the GALA data Teva conducted additional analyses on disability progression in both arms over two and three years of duration. Using a generalized estimating equation model that adjusted for baseline EDSS and number of relapses in the two years prior to GALA, it was estimated, based on 24 months and 36 months of follow-up data for Copaxone® 40 mg TIW from the GALA extension study, that the corresponding

disability RR (early start vs delayed start) estimates are: 24 months = 0.81 (95% CI 0.55-1.19); at 36 months = 0.78 (95% CI 0.59-1.05). We believe that these are conservative estimates of disability progression RR for Copaxone® 40 mg TIW compared with placebo since the delayed start (comparison) group was treated with Copaxone® 40 mg TIW for one out of the two years for the 24 month and two out of the three years for the 36 month estimate. This provides further face validity to our proposed approach of considering the disability progression RR estimate for Copaxone® 40 mg TIW to be equivalent to that estimated for Copaxone® 20 mg QD (RR=0.70; 95% CI 0.54- 0.93).

Use of these supplemental data is consistent with the evidence used by leading health authorities. The European Union (EU) regulatory agencies considered this comparison across study data, supporting the authorities to evaluate the value and patient benefit of providing access to Copaxone® 40 mg TIW as a therapeutic option (Cutter 2014a; Cutter 2014b; Giovannoni 2015).

Medication Discontinuation Rates

One of the Key Model Assumptions made in the Comparative Value assessment (as noted on page 61, Table 15) is a constant medication discontinuation rate of 10% per year for the first two years of therapy across health states and medications. A few considerations related to this topic are outlined below:

a. Notable heterogeneity is reported among the DMTs for the treatment of RRMS both in medication discontinuation rates (page 47, Table 11 of the ICER draft report) and in long-term safety profiles (Mikol 2008; O'Connor 2009).

b. The study cited (Tappenden 2009) in ICER's evaluation to arrive at a 20% withdrawal rate estimate over the first two years of treatment (i.e., 10% per year) for the included interventions does not reflect these observed differences.

We respectfully suggest that ICER reconsiders use of treatment-specific drug discontinuation rates in place of the current assumption of same discontinuation rates across all therapies. Not accounting for drug specific discontinuation rates in the analyses could further impact validity of cost-effectiveness analysis results.

Copaxone® and Glatopa®

ICER has included in its cost-effectiveness analysis Glatopa®, a generic version of Copaxone® 20 mg/ml. The clinical effectiveness parameters for Glatopa® used in the model are assumed to be identical to Copaxone® clinical trial results. We suggest that ICER considers in this analysis the findings of data recently presented (Kolitz 2016) and submitted to the FDA (https://www.regulations.gov/document?D=FDA-2007-D-0369-0395), highlighting differences between Copaxone® and Glatopa®, a generic version of Copaxone® 20 mg/mL.

Copaxone® is a synthetic complex polypeptide mixture that contains up to 10^{29} variants of polypeptides. Copaxone® physicochemical properties cannot be fully characterized. There is no

measurable pharmacokinetic profile, and no validated pharmacodynamic markers specifically identified and robustly validated to date. The active moiety(ies) are unidentifiable within the active substance. Furthermore, the manufacturing process is extremely sensitive to minor changes in reaction conditions and specifications. Glatopa®, the first generic glatiramer acetate product, was recently approved in accordance with the criteria set forth in FDA Draft Guidance on Bioequivalence of glatiramer acetate. Results of a battery of rigorous scientific tests on multiple commercial batches of Glatopa® demonstrate that there are compositional and biological differences between Glatopa® and Copaxone® across multiple physicochemical attributes as well as inflammatory and immune-related pathways. Teva has submitted its comments to the FDA Draft Guidance, which includes a comprehensive description of the new comparative scientific data available on Glatopa® (https://www.regulations.gov/document?D=FDA-2007-D-0369-0395).

We respectfully request that ICER consider the above suggestions in finalizing the evidence report.

Sincerely,

Sanjay Gandhi, PhD

Sr. Director, Global Health Economics and Outcomes Research
Global Medical Affairs
on behalf of Teva Pharmaceuticals

References

Comi G, Cohen JA, Arnold DL, Wynn D, Filippi M; FORTE Study Group. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. *Ann Neurol*. 2011;69(1):75-82.

Cutter G, Wolinsky J, Comi G, et al. Comparable clinical and MRI efficacy of glatiramer acetate 40mg/mL TIW and 20mg/mL QD: results of a systematic review and meta-analysis. Presented at ACTRIMS-ECTRIMS meeting on 11 September, 2014(a), Boston, Massachusetts.

Cutter G, Wolinsky J, Comi G, et al. Indirect comparison of effects of glatiramer acetate 40-mg TIW and 20-mg QD dosing regimens on relapse rates: results of a predictive statistical model. Presented at ACTRIMS-ECTRIMS meeting on 11 September, 2014(b), Boston, Massachusetts.

European Medicines Agency (EMA). Clinical investigation of medicinal products for the treatment of multiple sclerosis. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001169.jsp&mid=WC0b01ac0580034cf5. Accessed October 19, 2016.

Giovannoni G, Brex P, Sumra M, Walters E, Schmierer K. Glatiramer acetate slows disability progression – results from a 6-year analysis of the UK Risk Sharing Scheme. Presented at ECTRIMS meeting 7-10 October 2015, Barcelona, Spain.

Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R; GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann Neurol.* 2013;73(6):705-713.

Khan O, Rieckmann P, Boyko A, et al. Efficacy and safety of a three-times-weekly dosing regimen of glatiramer acetate in relapsing-remitting multiple sclerosis patients: 3-year results of the Glatiramer Acetate Low-Frequency Administration open-label extension study [published online ahead of print August 8, 2016]. *Mult Scler*. 2016.

Kolitz S, Laifenfeld D, Fowler KD, Hasson T, Konya A, Bakshi S et al. Similarities and differences in the gene expression profiles of Glatopa® and Copaxone®. Presented at ECTRIMS meeting 15 September 2016, London, England.

Medicines and Healthcare Products Regulatory Agency (MHRA). Public assessment report: Copaxone 40 mg/ml solution for injection, pre-filled syringe (glatiramer acetate). http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con521776.pdf. Published March 12, 2015. Accessed December 19, 2016.

Mikol DD, Barkhof F, Chang P, et al; REGARD study group. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol*. 2008;7(10):903-914.

National Institute of for Health and Care Excellence (NICE). Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. Technology appraisal guidance. Published: 23 January 2002 nice.org.uk/guidance/ta32

O'Connor P, Filippi M, Arnason B,et al; BEYOND Study Group. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. *Lancet Neurol*. 2009;8(10):889-897.

Sormani MP, Bonzano L, Roccatagliata L, Mancardi GL, Uccelli A, Bruzzi P. Surrogate endpoints for EDSS worsening in multiple sclerosis. A meta-analytic approach. *Neurology*. 2010;75(4):302-309.

Tappenden P, McCabe C, Chilcott J, et al. Cost-effectiveness of disease-modifying therapies in the management of multiple sclerosis for the Medicare population. *Value Health*. 2009;12(5):657-665.

MS Coalition Comments

ICER Draft Evidence Report

Disease-Modifying Therapies for Relapsing-Remitting and Primary Progressive MS

The MS Coalition commends ICER for the comprehensive review of the current disease-modifying therapies in the Draft Evidence Report. However, there was overwhelming consensus that the authors took considerable liberty comparing across trials that do not have comparable populations and extrapolating from old natural history studies. The report does identify and discuss some of the problems with mixing old and new data but in some cases, this issue is not adequately addressed. For example, (page 2) the authors make the important point that populations changed over time, making trial populations less comparable—yet they proceed with the comparisons. Specifically, the report acknowledges the substantial time span of the trials (1987-2015), the use of different definitions of MS, the use of different inclusion criteria, the use of different outcome definitions, and so on. Yet there is no indication that any adjustment or analysis using these factors was made when generating the results, and no mention of study heterogeneity is made in the presentation of the results as forest plots, league tables, etc.

The lack of reliable estimates of disease progression in naïve patients is a major limitation for estimating the cost-effectiveness of MS treatments. These considerations make the comparative efficacy conclusions in the analysis unreliable.

The report does not take into account the use of more potent agents as first line therapies. In addition, the model does not account for more than one switch of therapy due to breakthrough disease. The projected number of relapses (page 69) is not realistic given current accepted medical practice. Further, extrapolation of clinical trial data which is limited to 2 years or less does not provide support or validation of assumptions made in the report.

It is not clear how indirect costs were included in the model. For example, on page 4, indirect costs are not included despite the high impact of these costs cited in the background. Further, the term, 'best supportive care' is used as a comparator yet no definition or citation is provided. This term must be clearly defined with costs allocated.

The use of generic glatiramer acetate 20 mg as the universal comparator is unsupported by any human data. The product has not been studied in a clinical trial, has modest efficacy on relapses and MRI (using brand-name GA 20 mg) and lacks data demonstrating prevention of disability progression.

Figure 4 shows GA 20 mg with better disability outcome than teriflunomide. However, two large trials of over 1,000 patients each have shown teriflunomide's positive benefit on disability and one smaller trial of GA failed to show a significant benefit on disability. These results are inconsistent with the reports statement, "Finally, our NMA suggested that interferons, glatiramer acetate, and teriflunomide were substantially similar with respect to their effects on ARR and disability progression."

The conclusion that generic GA 20 mg was favored as a 'good value' gives a green light to make generic glatiramer acetate the first-line favorite by insurance companies/pharmacy benefit managers. The assumptions made on its performance (negative treatment effects) appear to be from a model-based assessment and are inconsistent with other published data.

There is limited data available on daclizumab, particularly related to long term effects. However, the authors are less cautious in declaring daclizumab safe than for ocrelizumab.

The conclusion that generic glatiramer acetate and alemtuzumab are most cost effective has significant negative implications for the availability of MS treatment options. This conclusion is nullified if rituximab (actually the lowest cost generic) is used instead as the comparator.

Another limitation of the report is the lack of strong data on patient reported outcomes which the authors acknowledge are most important to people living with MS. The importance of shared decision-making between people living with MS and their clinicians cannot be overstated in the report as an individualized treatment plan is the singular path to achieving both the best results of maximizing efficacy and adherence and achieving individualized goals for each person living with MS.

Additional Comments Related to Methodology/Analysis

Costs and Sensitivity Analysis

There are concerns with some of the assumptions and references used on the cost side of the analysis. The costs have a source but it might be important to have multiple sources to attempt to better understand the real cost sides. The sensitivity analyses show just how imprecise the results are and thus, it leaves any interpretation pretty wide open to comment/criticism.

Classification of Quality of Studies

While the need for certain measurements for this purpose is important, the lack of measurement of one of the key outcomes is not necessarily a quality issue and may encourage the reader to discount a particular study when the study itself is of high quality but may not be of particular utility for this undertaking.

12 Week Confirmation Rates

There is a fundamental flaw in using the 12-week confirmation rates without adjustment—even a ratio adjustment could be made but this scrambles the expected relationship between the relapse rates and CDP rates and falsely raises the CDP compared to the 24 week data as it has been well shown that 12 week CDP is higher than 24 weeks. The estimated increase over placebo by GA 40 mg seems inconsistent with data presented to date (page 40).

Bayesian Methodology

The use of the credible interval is reasonable (page 41) but the assumptions of the Bayesian methodology and how MCMC borrows information in the face of the previously described time trends needs a bit more discussion. One solution to understanding would be to repeat the NMA studies after 2008 to see how many of the conclusions depend on the earlier data, where the

definitions of relapse were looser, the populations potentially sicker, certainly with longer duration of disease.

Trial Discontinuation Rate

The rationale for the 10% trial discontinuation rates for all drugs is not reasonable. The discontinuation rates for Tecfidera are much higher than others and this should factor into the model in some way.

Mortality Multiplier

The mortality multiplier is based on 1997 data which antedates the treatment era as well as not reflecting the current diagnostic criteria. It is possible that milder cases are being included today in cohorts because there are treatments that can be offered whereas in the era before formal DMT's, little was offered and the milder cases may have been ignored or not labeled. There are at least 4 datasets that provide mortality data that might be used to inform this.

Utilities

The utilities come from two related studies and may not be as generalizable as might be desired.

In summary, we commend the considerable effort involved in compiling the available evidence and conducting the analyses described in this report. However, as noted above, several of the choices made in the NMA analysis and cost-effectiveness model significantly undermine our confidence in the results. We also wish to emphasize that due to heterogeneity in treatment response, safety and tolerance, and individual preferences, none of the currently available MS DMTs will be beneficial and appropriate for all MS patients, but each DMT will be beneficial and appropriate for some patients. We would appreciate seeing this point reinforced in the report, with support given for access by patients and physicians to all DMTs without undue restrictions on the part of payers.

Thank you for the opportunity once again to offer our collective comments on the ICER report.

Respectfully Submitted on Behalf of the Nine Member Organizations of the MS Coalition,

Lisa Skutnik PT, MA, MA
President, MS Coalition

MS Coalition Members:
Accelerated Cure Project
Can Do Multiple Sclerosis
Consortium of MS Centers
International Organization of MS Nurses
Multiple Sclerosis Association of America
Multiple Sclerosis Foundation
MS Views and News
National Multiple Sclerosis Society
United Spinal Association

National
Multiple Sclerosis
Society

December 21, 2016

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
Boston, MA 02109

Submitted via email: publiccomments@icer-review.org

RE: Public Comment on Draft Evidence Report Disease-Modifying Therapies for Relapsing-Remitting and Primary Progressive Multiple Sclerosis: Effectiveness and Value and Draft Voting Questions

Dear Dr. Pearson,

The National Multiple Sclerosis Society (Society) appreciates the opportunity to submit comments on the Institute for Clinical and Economic Review's (ICER) draft evidence report, *Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value*. Multiple Sclerosis (MS) is an unpredictable, often disabling disease of the central nervous system that disrupts the flow of information within the brain, and between the brain and body. The Society works to provide solutions to the challenges of MS so that everyone affected by this disease can live their best lives.

We commend ICER on their review of the MS medication class and for seeking to bring economic clarity to this expensive class of medications. High prices, along with increased out-of-pocket costs for people with MS, inconsistent formularies across different insurers, lack of price transparency and complex approval and appeals processes often create barriers to people with MS accessing the right treatment for them. The Society's "Make Medications Accessible" Initiative seeks to find solutions to these challenges with all stakeholders involved in the healthcare system. We hope that ICER's final evidence report can bring value to these important conversations.

We found the analysis of the clinical trial evidence to be a thorough summary of disease modifying therapies (DMTs) approved for use in the United States (U.S) market. We were also pleased to see some incorporation of the learnings ICER accumulated from outreach to people living with MS, patient advocacy groups, healthcare providers and other stakeholders. These included recognition of the economic burdens facing people with MS, a desire for patient-reported outcomes and the critical importance of shared decision making with their healthcare provider to ensure treatment choices that meet individual needs. However, not enough attention is paid to the heterogeneity of MS and the differences in the mechanisms of action associated with the DMTs, which are of high importance when choosing treatment. The type of analysis that ICER attempts is commendable; however, it is dependent on many variables that are further complicated by the heterogeneity of MS,

the variable individual response to medication, and a large number of quality of life factors. Studies show that <u>early and ongoing treatment with a DMT effectively modifies the course of the disease, prevents the accumulation of disability and</u> <u>protects the brain from damage</u> due to MS[1] [2]. As such, we believe that a full range of treatment options should be available to every person living with MS, so that they - in collaboration with their health care providers - can make informed treatment decisions. Further, any person who is stable on a DMT <u>should not be forced to switch</u> to another agent because of changes in medication coverage or cost considerations. A delay in treatment can have a negative and permanent result.[3] [4]

In our review of the draft evidence report, the Society has outlined some areas that need to be re-evaluated for accuracy and to improve the usefulness of the document. Some of the below inaccuracies are regarding alemtuzumab and glatiramer acetate, both of which figure prominently in the review and conclusions as a cost effective treatment and baseline treatment respectively.

- Within Table 1, ICER has listed alemtuzumab's dosage as 12 mg per day for 3 days every year. The label for alemtuzumab, marketed as Lemtrada, states that the drug should be administered for 5 days at baseline, and then for 3 days a year later. Additional doses are only administered after that with new disease activity.[5]
- The American Academy of Neurology Draft Guidelines do not recommend testing for antibodies to John Cunningham virus (JCV) in patients taking fingolimod or dimethyl fumarate nor avoidance of these drugs in patients with JCV antibodies.[6]
- ICER reports the CONFIRM trial of glatiramer acetate and dimethyl fumarate versus placebo as a head to head trial: however, the CONFIRM trial was not powered as a head to head assessment.[7]
- The authors state that alemtuzumab was consistently better in preventing disability progression; however, in the Care-MS1 trial, there was no significant difference between the alemtuzumab and IFNB-1a in preventing disability progression.[8]
- Natalizumab, when compared to a generic glatiramer acetate, was given a B+ rating-however, the accompanying table (Table 13) had its designation listed as a C+.
- In the U.S., alemtuzumab has a strong recommendation from the FDA to be used as a third-line therapy; however, within the review, the authors repeatedly refer to it as a second-line therapy.[9]

Current Limitations of the Draft Evidence Report
While the Society appreciates ICER's thorough review, we are concerned by assumptions made within the document, the scientific validity of the comparisons used and the resulting value conclusions. Insufficient attention is paid to the heterogeneity of the MS population, quality of life factors and variable response to treatments. In the survey of people with MS, 90% rated continuing working/normal activities as important/very important- behind only delaying disability and preventing relapse (Table 3). The authors state this echoes what they heard from individual patients and patient advocacy groups, yet this doesn't have a corresponding emphasis in the analysis. In our view, the report also draws incorrect conclusions from the widely differing opinions on treatment guidelines (American Academy of Neurology, Canadian Agency for Drugs and Technology in

Health, MS Coalition and National Institute for Health and Care Excellence) and the range of coverage policies by payers. The range of these guidelines and policies indicates the need for differing options due to the heterogeneity of MS. **Reviews like ICER's that look at cost effectiveness may be used to limit access to DMTs for people living with MS. Therefore, we believe it is critical that ICER acknowledge the limitations of the review and clearly point out the many assumptions that were made that potentially undermine the validity of the cost conclusions.**

We remain concerned that the comparisons that ICER used to evaluate the different treatment trials are based on data that are more than two decades old. These data and the study populations for older therapies do not represent modern populations or current practice. People entering trials for relapsing remitting (RRMS) MS for the older therapies were generally in a later state of disease than those currently entering RRMS trials due to improved diagnostic tools. Further, the randomized controlled trials (RCT) only show data over a relatively short time frame (usually a maximum of 2 years). Beyond that time period, there is very limited data available to validate the assumptions that ICER makes in the document**. Given these significant study population differences, the RCTs are not directly comparable, thus making the resulting comparative efficacy conclusions in the analysis unreliable.** ICER acknowledges the challenges of trying to compare therapies based on registration trials, but does not adequately account for this challenge in the result and cost-analysis. The lack of reliable estimates of MS progression in newly diagnosed patients is another major limitation for estimating cost effectiveness of MS treatment modalities; its implications on the results of any predictive modeling need more attention in the review.

Additionally, the review makes the assumption that a person with MS goes off treatment after failure with second-line therapies. This assumption is not consistent with current medical practice or payer policies. There are many reasons why someone may need to switch to another DMT after the second therapy: allergy, adverse side effect (e.g. laboratory abnormalities), new contraindication, etc. While many people with MS will take more than one DMT throughout the course of the disease, it is also common for people to take more than one medication that ICER refers to as first-line before moving to a medication that ICER refers to as second-line. Often, this is due to payer policies. People with MS may also take more than one of the "second-line" therapies. These assumptions should be changed in the final review to reflect current practices.

The draft evidence report also lacks reliable data on patient reported outcomes, which as the authors state (Table 3) are the most important outcomes for patients. Furthermore, the utility data that the authors used in their modeling came primarily from non-U.S. studies. Utility data are known to be reflective of cultural and societal preferences, therefore it is likely that these data do not represent the true preferences of a person in the U.S. who lives with MS. Changes in relapse management, as well as other healthcare delivery changes are also likely to affect costs.[10]

In our review, it appears that indirect and direct health costs are missing health expenditures that are common for people with MS. For example, when a person with MS switches or begins a new DMT,

this often requires additional physician visits for medication adjustments and side effect management. Regular MRIs may also be used to monitor or assess DMT effectives.

Possible Areas of Improvement for Final Evidence Report and Final Voting Questions
The Society has outlined several areas that the authors should reevaluate in the final evidence report. We believe that these revised components will improve the review for providers and people living with MS.

- The authors should reconsider the exclusion of clinically isolated syndrome studies as the implications of treatment decision on people with this early form of MS are particularly important. [11] [12] [13]
- ICER should reconsider their projected number of relapses on page 69 to better align with modern treatment guidelines.
- Ocrelizumab, to date, has not received approval from the Food and Drug Administration (FDA), and is unlikely to be approved prior to the review of this report; therefore much information concerning benefit/risk and price is speculative. The authors should reevaluate the information contained in the review on ocrelizumab once FDA's approval decision is made and more precise data and pricing information on the drug is known.
- It is currently unclear how the model used calculates and allocates indirect costs. More details on components used to calculate indirect costs and how they are valued is needed to truly identify and present cost. In addition, it would enhance confidence in the model if ICER were to publish the details of the model in a peer-reviewed publication.
- The economic evaluation that the authors utilize (Table 20) is based on a single NARCOMS survey from 2004. The prices of all MS therapies and reimbursement amounts for services and delivery have changed dramatically since that time. The authors should note in the final evidence review how their economic evaluation accounts for price differences since 2004 and how associated healthcare costs were estimated for other DMTs which were not available in 2004.
- Real world practice and treatment should be factored in with the cost analysis. For example, alemtuzumab is FDA approved as a third-line therapy. FDA makes a strong recommendation in the labeling that this treatment is to be used only after inadequate response to two or more DMTs. Thus, even though the review rates it as cost effective, this treatment is likely not an available option for many people with MS due to the labeling information and medical practice.
- ICER should add an answer choice of "insufficient data" to their draft voting questions. The limitations of the review impact the efficiency and cost conclusions drawn and currently there is a lack of scientifically validated data to answer the questions posed.

As ICER moves to finalize its review and voting questions, the Society believes it is important to acknowledge the benefit of this type of analysis to inform providers and people affected by MS about the full spectrum of approved treatment options. **The heterogeneity of the MS population and the clinical variability of MS between individuals make access to the full range of therapies critically important.** Treatment that may be effective and well tolerated in one may fail in another person, and people with MS may utilize several treatments in their lifetime. We believe

that individualized treatment plans, created by shared decision making between people with MS and their physicians will produce the best result and cost effectiveness by maximizing efficacy and adherence, while balancing risk tolerance.

On behalf of the National MS Society, thank you for your consideration of our comments, which we hope will improve the final evidence review. If you have any questions, please contact Leslie Ritter, Senior Director, Federal Government Relations at leslie.ritter@nmss.org or 202-408-1500.

Sincerely,

Bari Talenti, Esq.
Executive Vice President, Advocacy
National Multiple Sclerosis Society

[1] Kavaliunas A, Manouchehrinia A, Stawiarz L, et al Importance of early treatment initiation in the clinical course of multiple sclerosis. Mult Scler. 2016 Oct 17. pii: 1352458516675039. [Epub ahead of print]

[2] Kappos L, Edan G, Freedman MS et al. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. Neurology. 2016 Sep 6;87(10):978-87. Epub 2016 Aug 10.

[3] Kappos L, Freedman MS, Polman CH, et al. Long-term effect of early treatment with interferon beta-
1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of thephase 3 BENEFIT trial. Lancet Neurol. 2009;8(11):987-997.

[4] Penner I-K, Stemper B, Calabrese P, et al. Effects of interferon beta-1b on cognitive performance in
patients with a first event suggestive of multiple sclerosis. Mult Scler. 2012;18(10):1466-1471.

[5] Sanofi Genzyme. *Lemtrada Prescribing Information*.
http://products.sanofi.us/lemtrada/lemtrada.pdf. (Accessed Dec. 19, 2016).

[6] American Academy of Neurology. "Assessment: The Use of natalizumab (Tysabri)) for the treatment of multiple sclerosis (an evidence-based review).
http://www.neurology.org/content/71/10/766.full.pdf. (Accessed Dec. 19, 2016)

[7] Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1087–1097. https://www.ncbi.nlm.nih.gov/pubmed/22992072. (Accessed Dec. 19, 2016)

[8] Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012 Oct 31.
https://www.ncbi.nlm.nih.gov/pubmed/23122652. (Accessed Dec. 19. 2016)

[9] Sanofi Genzyme. *Lemtrada Prescribing Information*.http://products.sanofi.us/lemtrada/lemtrada.pdf. (Accessed Dec. 19, 2016).

[10] Kobelt G, Berg J, Atherley D, Jönsson B. Costs and Quality of Life in Multiple Sclerosis A Cross-Sectional Study in the USA Stockholm School of Economics in its series Working Paper Series in Economics and Finance with number 594; 2004.

[11] Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. Lancet. 2009;374(9700):1503-1511.

[12] Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology. 2006;67(7):1242-1249

[13] Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain J Neurol. 2008;131(Pt 3):808-817.

Hi, I have had RRMS since 1990. I am a RN and had to stop working in 2013. I am almost 49 years old. I read over some of your materials and have some thoughts. I'm not sure how beneficial they are, but do hope you read this and there is some consideration.

I have been on numerous DMTs since 1997 and do think it is beneficial to consider them and which is more effective. However, my big question is, does decreasing relapses really effect disability? I think I'm kind of young to be out of work. Believe me, relapses can be awful, but i think we need to think of this?

Also, maybe more importantly, i have asked for antibodies at least twice, to be told insurance doesn't cover it. So stupidly, i never had it done. I thought it was not a good thought. However, i had two big relapses last year while on Tysabri for over two years and one every year before that, the same as prior to being on that med.   I thought is was the strongest med. I do realize this is a progressive disease, and know it does work for some people (for relapses...I don't know statistics on disease progression) but it did not work for me. So after much research, i talked to my neurologist and discontinued it, with my last infusion March 20, 2016. I started non-traditional therapy and have not had a relapse in a year. I started the anti-inflammatory diet 4/15/16, LDN 5/20/16, and hormone therapy 8/22/16. I have not had a relapse in one year. The insurance does not cover these, so i pay cash out of pocket even though i am on a limited income now. So my insurance payed $10,000 a month but wont cover $100 a month. This does not seem right. And i still have not had antibody testing, but in my mind i feel those meds didn't work for me but this method is.

So perhaps we need to consider voting on some additional questions? Please consider and maybe respond to me as well. I am willing to help in any way. I don't think insurance companies shouldn't cover certain meds, because I'm telling you, a person is willing to try almost anything when they are very sick, and if insurance says they won't cover something, that is not fair. Should a doctor have knowledge of drug superiority, yes, and he should share the knowledge with the patient, but drugs should all be covered. Maybe certain ones only after others have failed? But then again, are we messing with the disease process? Maybe that's why antibodies are important?

Thanks,
Lisa Carr
(Patient Advocate)

Where is the research for patients who have decided to NOT to DMDs because they really don't work and only have to have 30% efficacy to be approved by the FDA not to mention the side effects by introducing a "decoy" molecule to your body. A decoy may/may not be effective for a short time until the "decoy" does not work anymore. Oh, right, then patient goes on to yet another DMDs. Just makes no sense. What about the patients who have changed their diet, added key supplementation, increased exercise, reduced lifestyle stress, etc...and they are doing just fine without DMDs. Stop supporting Pharm and look for the root cause!

-Mary Holmstrand
(Patient Advocate)