www.ms-coalition.org

February 14, 2014

Janet Woodcock, MD
Director, Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

Re: Implications of Alemtuzumab Decision for Multiple Sclerosis Community

Dear Dr. Woodcock:

On behalf of the Multiple Sclerosis Coalition (Coalition), I am writing to express our continued concerns regarding the Food and Drug Administration's (FDA or Agency) actions with regards to Genzyme Corporation's supplemental Biologics License Application for alemtuzumab as a treatment for relapsing forms of MS. You've already heard from several of our member organizations, but we are now writing to you to express our shared perspectives on this matter. The MS Coalition is a collaborative network of independent MS organizations whose vision is to improve the quality of life for those affected by MS. Our mission is to increase opportunities for cooperation and provide greater collaboration to leverage the effective use of resources for the benefit of the MS community.

After the Agency issued its Complete Response Letter to Genzyme, we heard from MS patients, providers and researchers that this decision, which is viewed by the community as a denial of marketing approval, not only inhibits access but also has larger ramifications for the MS research community. Below we outline our specific concerns related to both potential problems.

Restricted Access to a New Therapy

1. Benefit-Risk Considerations for People Living with MS

Since the FDA's announcement of its decision in December, our member organizations have received a number of calls of concern and disappointment from both the medical and patient community. In addition to these direct communications with our member groups, we have also discovered online petitions and polls regarding the denial. Most of these communications express that a number of individuals living with MS still have no available treatments and that there is a desire for greater consideration of the patient's risk tolerance and physician autonomy.

A person living with MS wrote the National Multiple Sclerosis Society, expressing her profound disappointment with the decision:

> *"This drug is a "game changer" for MS patients. I do not use that term loosely. My own personal experience with alemtuzumab resulted in a life exacerbation free since 2010….I feel so strongly about this medication, I went to the open Public hearing (at my own expense) to speak…Unfortunately, the approving committee wasn't able to hear from those of us who use this drug and chose to focus on things that were more punitive to Genzyme rather than looking at the 10-year history of this drug in treating MS."*

Additionally, the National MS Society and Consortium of Multiple Sclerosis Centers administered a collective poll to 1,550 prescribing clinicians about this issue (see attached for complete survey report). Summarizing the sentiment of many clinicians, one physician stated:

> "*Having participated in the trial and having seen the improvement and stability of my patients who had significant markers for aggressive MS, I am saddened and disappointed that the FDA did not recognize the benefit this medication would provide to those who are threatened with severe disability due to their disease status.*

As a coalition, we echo the concerns that were stated by patients and doctors. Because of the unique nature of the disease, a diagnosis of multiple sclerosis means different symptoms and challenges for each individual. As a result, the perceived benefits and risks vary case-by-case depending on the progression of the patient's disease and ability to tolerate available treatments.

It is our understanding that traditional benefit-risk assessment is rooted in weighing acceptable risks across a broad range of patients for a drug assessment. Because of the heterogeneity of the MS population, this historical framework is difficult to apply for these patients. On an individual level, many patients without other options are willing to take greater risks and we believe these patients' point of view should be captured as the Agency considers new drug applications. We know that the FDA is currently working on patient-focused drug development and the MS community would welcome a larger conversation with the Agency around this topic.

2. Potential Dangers of Medical Tourism for Alemtuzumab

It has been our past experience that people who have failed all of the existing treatments are likely to travel to other counties to seek alternative treatment options. Therefore, we fully expect (and have already heard) that patients are considering whether to travel internationally to receive alemtuzumab, especially because it has been approved by a number of other countries, including Australia, Canada, Mexico and nations of the European Union. This raises concerns about the after-care of individuals who seek alemtuzumab outside the US, since they will not be systematically tracked. Because the potential for adverse events with this medication could arise for many years, we are extremely anxious that a Risk Evaluation and Mitigation Strategy (REMS) will not be available to Americans living with MS and their safety could be compromised.

We appreciate that medical tourism is not a specific regulatory consideration for the FDA in this context. However, we do believe that it is a relevant consideration as the agency considers the Genzyme Corporation's appeal of the Complete Response Letter.

Global Implications for MS Research and Therapy Development

1. Advisory Committee Outcomes

Our community continues to be concerned by the confusing manner by which the FDA solicited advice from advisors at the November Advisory Committee hearing for alemtuzumab. As some of our member organizations expressed in earlier communications, the FDA failed to instruct the Committee about how the final discussion questions were worded and ordered, prior to voting and group conversation. This led to contradictory recommendations from the Committee about the safety and effectiveness of the alemtuzumab. We ask the Agency to carefully review the voting process employed at the Advisory Committee meeting and to give due consideration to the interests of people with MS during its decision process.

2. Outcome Measures and MS Therapy Development

The Coalition is also concerned by what appears to be a shift by the Agency regarding the validity of the Expanded Disability Status Scale (EDSS) as an outcome measure in MS clinical trials and the use of rater-blinded trial designs

With regards to the EDSS, we remain concerned by what appears to be a change in the Agency's position regarding this outcome measure. During the November Advisory Committee hearing on alemtuzumab, the FDA staff presentation aggressively questioned the usefulness of the EDSS even though it has been effectively mandated by the FDA and used in every pivotal clinical trial of disease modifying treatments for MS that have been approved by the FDA. It is also unclear if the Advisory Committee is aware of the central role that the EDSS has played in MS therapy development. While the EDSS has well known limitations as an outcome measure, it has not been criticized as a biased observation subject to patient and clinicians beliefs about therapies. Given that the EDSS is currently being widely used by sponsors in pivotal clinical trials, we worry that the Agency's staff presentation could have unintended consequences for MS therapy development by creating confusion regarding the FDA's view of this outcome measure. We ask that the Agency clarify its view on the use of EDSS in pivotal clinical trials of therapies for MS.

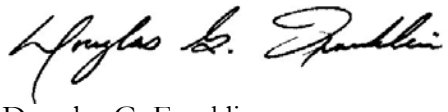
In addition we are concerned by the mixed signals being conveyed by the agency regarding rater-blinded clinical trial designs. We note that previous to the application of alemtuzumab, the agency accepted rater-blinded trial design in the EVIDENCE trial, which was used to show superiority of Rebif® to Avonex®. With this trial design, the FDA later approved Rebif®. However, the rater-blinded design was pointed to numerous times during the Advisory Committee meeting as a significant flaw, which could have led to considerable bias in the alemtuzumab results. While we recognize that a double-blinded study is the optimal design, differing side-effects and routes of administration with proprietary devices make it difficult to follow this standard and may alter important comparative effectiveness designs. Since our community is not clear about FDA's previous decisions, we would appreciate if the Agency would clarify its approach to rater-blinded designs.

We recognize, however, that outcome measures and clinical trial study designs for MS studies are dynamic and complex topics that would benefit from dialog between all of the interested

stakeholders. The Coalition would be pleased to work with the Agency to develop a framework for such a dialog.

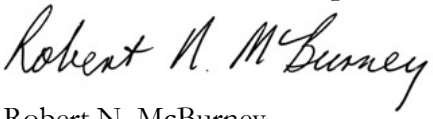
We would appreciate an opportunity to speak more in-depth about the concerns we outlined in this letter. You can reach me via email at dfranklin@MYMSAA.org or via phone at (856) 488-4500 ext. 112. We look forward to continued engagement with the Agency on this and other matters of interest to people living with MS.

Sincerely,



Douglas G. Franklin
President of Multiple Sclerosis Coalition
President and CEO, Multiple Sclerosis Association of America

Additional Coalition Co-signers below



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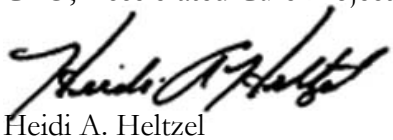

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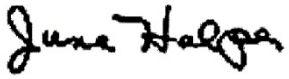

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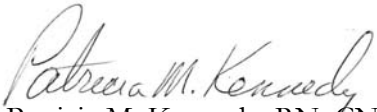

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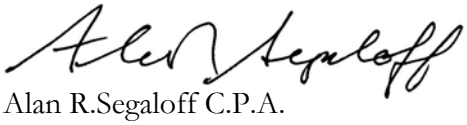

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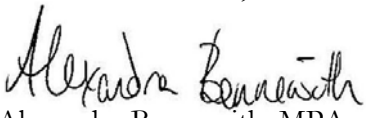


Alexandra Bennewith, MPA
Vice President, Government Relations, United Spinal Association

Results of Clinician Survey regarding FDA Lemtrada™ Decision

Background

In the weeks following the FDA's decision on Lemtrada, the National MS Society (Society) and Consortium of MS Centers (CMSC) were contacted by clinicians who wished to express their reactions and concerns. As is generally the case, those with the strongest opinions were the most likely to make contact. In an effort to get a clearer perspective on the broader range of opinions, the Society and CMSC collaborated on a survey to a collective mailing list of over 1,550 prescribing clinicians.

We received 151 responses for a response rate of 10 percent. The introductory demographics questions confirmed that we reached a diverse group of clinicians from different disciplines and varied practice settings and sizes. The vast majority (90 percent) routinely prescribe all available disease-modifying therapies.

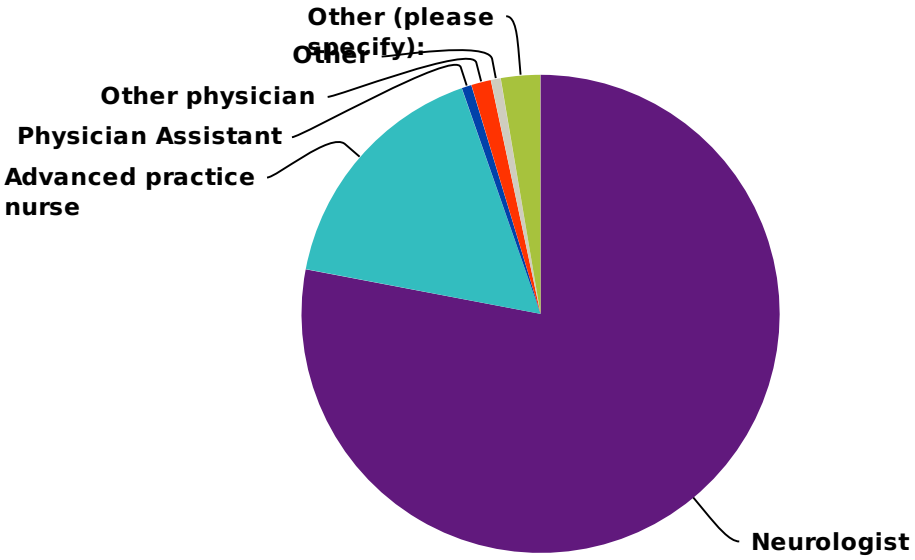
Of the respondents, approximately 23 percent agreed or strongly agreed with the FDA's decision and 77 percent disagreed or strongly disagreed with the decision. Clinicians offered a number of comments related to their responses and we have captured the themes, along with examples in the final section of this document.

THE CONSORTIUM OF MULTIPLE SCLEROSIS CENTERS

National Multiple Sclerosis Society

Q1 Are you a:

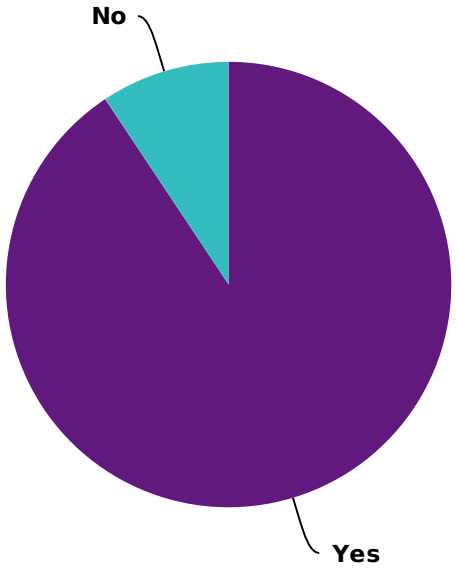
Answered: 150 Skipped: 1



Answer Choices	Responses	
Neurologist	**78%**	117
Advanced practice nurse	**16.67%**	25
Physician Assistant	**0.67%**	1
Other physician	**1.33%**	2
Other	**0.67%**	1
Other (please specify):	**2.67%**	4
Total		**150**

Q2 Do you routinely prescribe all FDA-approved disease-modifying therapies (DMTs), including natalizumab and all oral disease modifying medications?

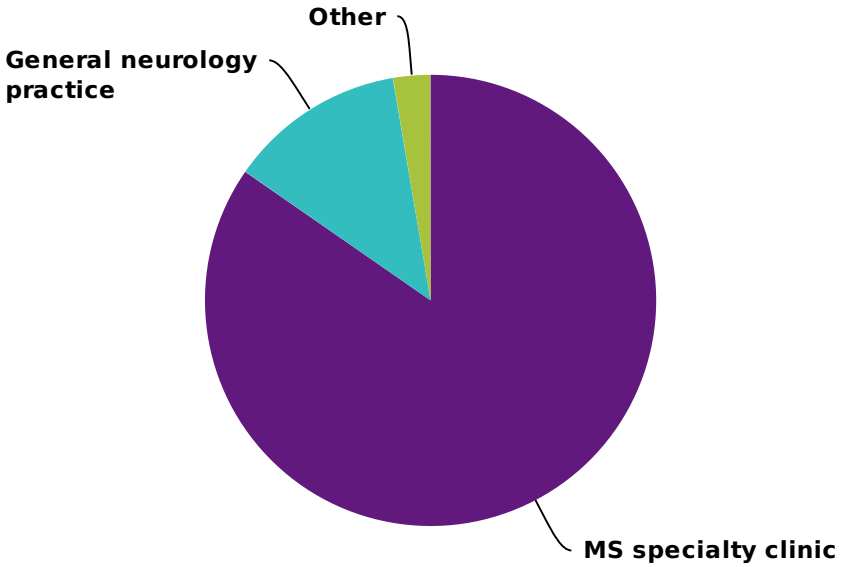
Answered: 150 Skipped: 1



Answer Choices	Responses	
Yes	**90.67%**	136
No	**9.33%**	14
Total		**150**

Q3 Indicate your primary practice setting:

Answered: 150 Skipped: 1



Answer Choices	Responses	
MS specialty clinic	**84.67%**	127
General neurology practice	**12.67%**	19
Other	**2.67%**	4
Total		**150**

Q4 How many MS patients are under your continuing care?

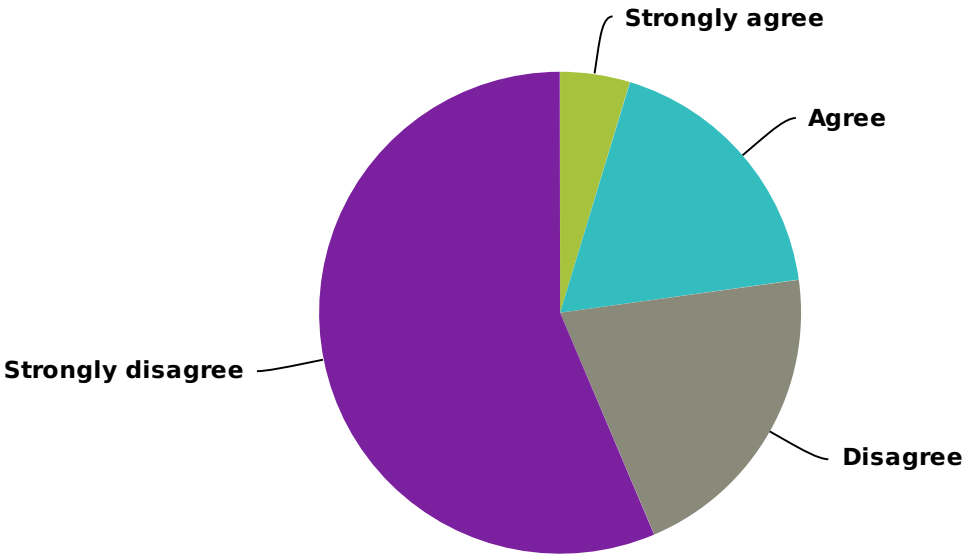
Answered: 142 Skipped: 9

A total of 142 clinicians responded to question 4 of the survey and collectively reported treating 96,085 individuals with MS. The number of MS patients treated ranged from 20 to 4,200. These responses reflect individual clinician data as well as total patients treated in a particular MS Center. Due to the variability in the interpretation of the question and total number of patients reported, it was decided that a graph would not accurately reflect the number of patients treated per respondent.

See Analysis of Comments Section

Q5 Do you agree with the FDA's decision regarding Lemtrada?

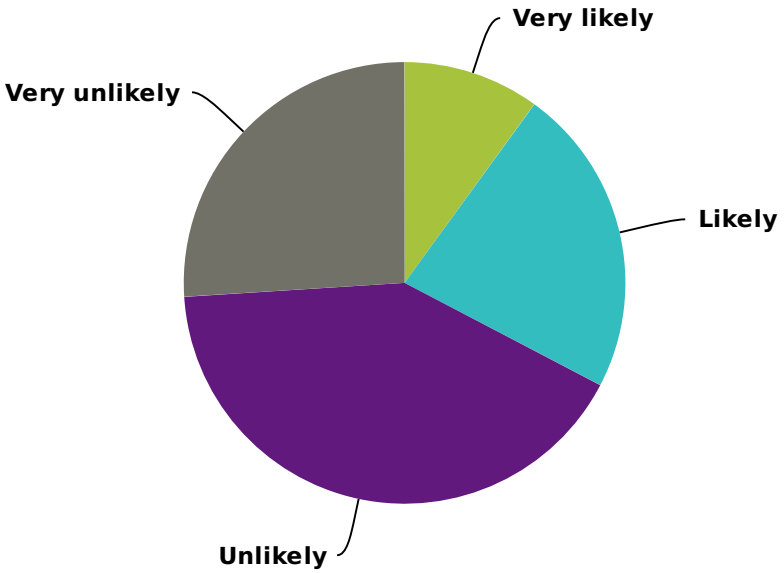
Answered: 149 Skipped: 2



Answer Choices	Responses	
Strongly agree	4.70%	7
Agree	18.12%	27
Disagree	20.81%	31
Strongly disagree	56.38%	84
Total		149

Q6 How likely are you to discuss with your patients the option of seeking treatment with Lemtrada outside of the U.S.?

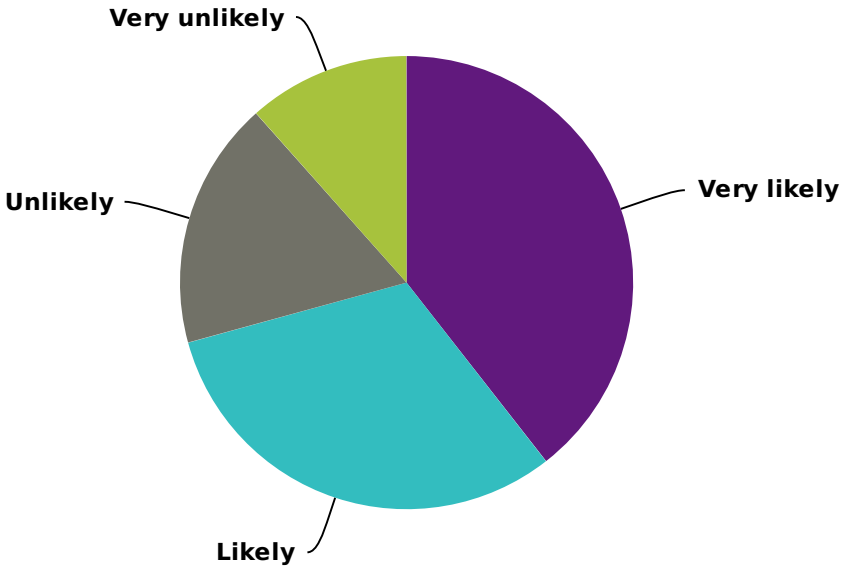
Answered: 150 Skipped: 1



Answer Choices	Responses	
Very likely	10%	15
Likely	22.67%	34
Unlikely	41.33%	62
Very unlikely	26%	39
Total		150

Q7 How likely are you to provide long-term monitoring for any patient who decides to obtain treatment with Lemtrada outside of the US?

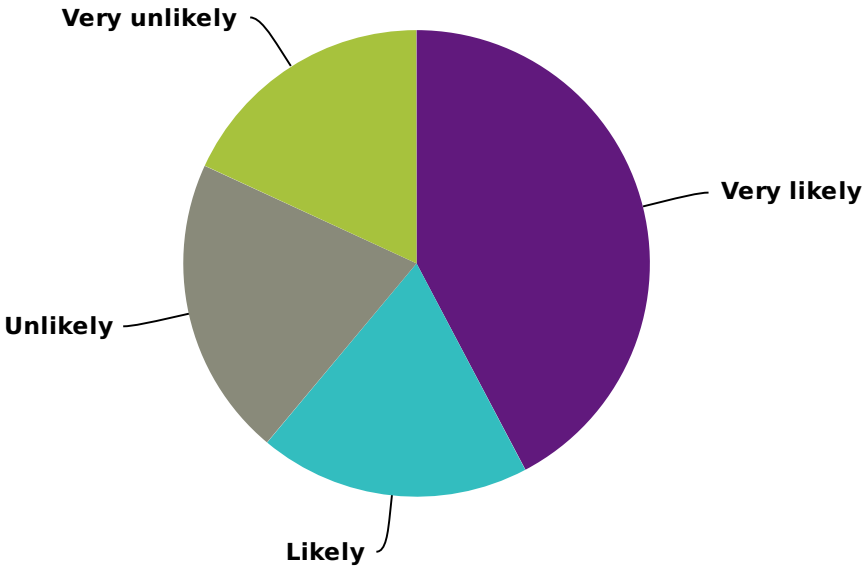
Answered: 147 Skipped: 4



Answer Choices	Responses	
Very likely	**39.46%**	58
Likely	**31.29%**	46
Unlikely	**17.69%**	26
Very unlikely	**11.56%**	17
Total		**147**

Q8 How likely are you to express your concern (either individually or through an organized response) to the FDA regarding its recent Lemtrada decision?

Answered: 149 Skipped: 2



Answer Choices	Responses	
Very likely	**42.28%**	63
Likely	**18.79%**	28
Unlikely	**20.81%**	31
Very unlikely	**18.12%**	27
Total		**149**

Q9 If you plan to express your concern, through what mechanism(s) or channel (s) are you most likely to do so?

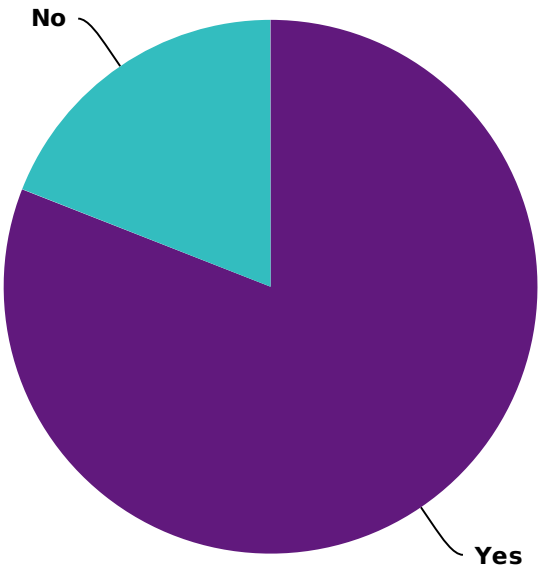
Answered: 81 Skipped: 70

Among the 81 responses to Question 9 the primary mechanism and channels mentioned included letters/emails to the FDA and/or congressmen, “surveys like this one”, petitions (physicians, investigators, patients), group/organizational responses (with several specifically calling out the Society, CMSC and AAN), media interviews, and encouraging patients to advocate. Some respondents indicated that they would use several methods while others indicated only one. Several clinicians indicated that they wanted to do something but didn't know how to go about it. And several indicated that they did not plan to do anything.

See Analysis of Comments Section

Q10 Do you think that the Lemtrada decision has implications for future MS drug development?

Answered: 147 Skipped: 4



Answer Choices	Responses	
Yes	**80.95%**	119
No	**19.05%**	28
Total		**147**

Q11 What advice do you have for the MS Coalition and its members regarding engagement with the FDA around this and/or other longer-term issues related to MS therapy development?

Answered: 98 Skipped: 53

There were 98 responses to Question 11, and the recommendations to the MS Coalition were quite varied. Some respondents believed that the FDA needs to hear/listen to the voice of MS experts about Lemtrada and leave risk/benefits decisions to the clinician and patient. Others believed that the focus of the Coalition should be on recommendations for more consistent guidelines regarding trial design, the composition of the advisory panel and the overall approval process. In addition there were a minority of respondents who recommended that the Coalition not respond to the decision, but rather focus on the safety of potential treatments for MS and not this decision.

See Analysis of Comments Section

Results of Clinician Survey Regarding FDA Lemtrada™ Decision

ANALYSIS OF COMMENTS

Question 5: Do you agree with the FDA decision regarding Lemtrada?

Agree/Strongly agree: 34 (23%)

Theme #1: Too dangerous to approve

- The level of efficacy is disappointing for the risk. additionally the extended patient follow up is concerning

Theme #2: Not enough scientific rigor to approve

- The problem is not the FDA. The problem is the trial did not meet the scientific rigor needed to show benefit. No one should rely on unblinded clinical trial to conclude efficacy

Disagree/Strongly disagree: 115 (76%)

Theme #1: Eliminates a potential option for select group of patients

- We have a small population of patients who are suboptimally controlled on the therapies currently available. These patients have very active disease, and feel strongly that potential benefits with alemtuzumab would outweigh the risks.
- While there are significant risks with alemtuzumab, there are also benefits for those with severe MS who have no other good options for various reasons (allergies, failed therapies, Nabs, etc.)"
- Having participated in the trial and having seen the improvement and stability of my patients who had significant markers for aggressive MS, I am saddened and disappointed that the FDA did not recognize the benefit this medication would provide to those who are threatened with severe disability due to their disease status.

Theme #2: Blinding not possible due to side effects of agents tested

- I have been an investigator in alemtuzumab trials for 10 years and feel that the active comparator study design was the most appropriate and valid design to be done. A fully blinded trial would be impossible given the obvious and prevalent infusion related reactions with the alemtuzumab.

Question 6: How likely are you to discuss with your patients the option of seeking treatment with Lemtrada outside of the U.S.?

Likely/Very Likely: 49 (33%)

Theme #1: Yes – for select patients

- There are patients who are candidates for alemtuzumab therapy, I am convinced of its benefits, and it is available in countries where the quality of clinical care is appropriate. It is an option they should pursue.
- Depending on the patient's resources, I would definitely consider this dialogue of making sure my patient received that I believe to be the best medication given their circumstance.

Unlikely/very Unlikely: 101 (67%)

Theme #1: No for safety reasons

- I will actively recommend that my patients do not get Lemtrada outside the US, as I think that raises potential safety issues. Long - term patient tracking (presumably would have been part of REMS if Lemtrada was approved) is an issue, especially for patients that may move or be in underserved areas. Also, I wonder if insurance would pay for this frequent monitoring of patients who received a drug that was denied by FDA.
- The reason is the follow-up monitoring and not being willing to provide long-term monitoring for any patient who decides to obtain treatment outside of the US

Theme #2: No for cost reasons

- I do not think this will be a financially feasible option for most of my patients for whom we were considering alemtuzumab.

Question 7: How likely are you to provide long-term monitoring for any patient who decides to obtain treatment with Lemtrada outside of the US?

Likely/Very Likely: 104 (71%)

Theme 1: I'll do it because it's my responsibility as a physician

- It would be hard not to do so, but in the absence of a risk management program in the US for non-US treated MS subjects this will be a very complicated problem with considerable fiscal/liability risk to the patient and treating physician who does so.
- If a patent has been given this drug, and comes to our clinic, we would be obligated to care for the patient as it is unlikely community neurologists would be comfortable doing so. Patient safety above all else.

Theme 2: U.S. patients were in the clinical trials

- We've got patients who were in the clinical trials so this is very disappointing

Unlikely/Very Unlikely: 43 (29%)

Theme 1: impossible/unrealistic

- Would never do this

Question 10: Do you think that the Lemtrada decision has implications for future MS drug development?

Yes – 119 (81%)

Theme 1: This decision by the FDA will impede progress in MS drug development:

- It is likely to discourage the development of extremely effective agents, which are needed for the small but significant population of patients refractory to other therapeutic agents, but which carry significant risk for serious adverse events
- This kind of thinking and decision making pattern on the FDAs part will inhibit and discourage both MS researchers and the industry in pursuing future MS drug research and development
- The FDA has now set an important precedent by allowing the completion of 2 large clinical trials then rejecting the drug application on the basis of clinical trial design. Who would want to invest the time, money, and patient experience in such a trial again?

Theme 2: Placebo-controlled trials are unethical and should be replaced by active comparator trials:

- I think that we have reached the stage in MS care that double blind, randomized, placebo-controlled phase 3 trials for new MS therapies are unethical. New trials should compare new agents against a standard, active therapy rather than a placebo.

No – 28 (19%)

Theme 1: This was a correct decision that will/should lead to more careful trial design, due diligence, and attention to FDA recommendations:

- The FDA is clearly concerned about unwarranted risk in an environment where many therapies are already available. Future therapies must tailor the treatment for the most appropriate population given the known or anticipated risks of that therapy. It is also important to tailor study designs appropriately. While well intentioned the comparison of Lemtrada to Rebif, particularly in patients who had previously not responded to an interferon was an ill-conceived study design.

Question 11: What advice do you have for the MS Coalition and its members regarding engagement with the FDA around this and/or other longer-term issues related to MS therapy development?

Theme 1: The FDA needs to hear/listen to the voice of MS experts about Lemtrada and leave risk/benefit decisions to the doctor and patient:

- ….I strongly recommend that statements be made explaining the position that doctors and patients are capable of using the drug appropriately, and that the reasons for denial were not based on efficacy or safety, but on dogma in trial design that is inappropriate
- …it seems that the FDA is focusing on issues that are less germane to our patients' disease management, and losing sight of the fact that they are denying MS patients another effective second line agent that may be useful for those who are currently breaking through on a first line therapy, and who may not be candidates for natalizumab.
- …I would raise concern over their ethics in allowing trials to go on when they are going to reject them based on trial design at the end of the day. These 2 phase [3] trial results were what was expected from the phase 2 results both in regard to benefit and safety (the most efficacious treatment to date). How could they let patients participate in this study with risk and time commitment if they were going to reject it with the expected outcomes being achieved?

Theme 2: Focus on the bigger, long-range picture:

- I would suggest that any engagement with the FDA not be about Lemtrada alone, but to use this as an example of conflicting guidelines about what constitutes an adequately done MS clinical trial. Also stress that there is an unmet need in MS patients with breakthrough disease activity on current therapies or who are at high risk of PML with current therapies.
- FDA has been very inconsistent about application process for reviewing and approving DMTs. This largely results from the different opinions and backgrounds of the members of the advisory panel. There needs to be a better representation of MS specialist in panels that are review DMTs.

Theme 3: The MS Coalition should stay out of this:

- The MS Coalition should not be advocating for release of all drugs shown to be effective without consideration of safety. The registration of mitoxantrone for treating MS was a major mistake and has resulted in the death of a number of people with MS. The MS Coalition should be as concerned about safety as it is about efficacy.