CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761029Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA #/Supplement #	761029
Applicant Name	Biogen
Date of Submission	2/27/15
PDUFA Goal Date	5/27/16
Proprietary Name/ Established (USAN) Name	Zinbryta/daclizumab
Dosage Forms/Strength	Injection/150mg
Proposed Indication(s)	Treatment of relapsing forms for multiple sclerosis
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	Laurie Kelley, PA-C
Medical Officer Review	Larry Rodichok, MD; Lourdes Villalba, MD
Statistical Review	Xiang Ling, PhD
Pharmacology Toxicology Review	Dave Carbone, PhD
CMC/OBP Review	Joel Welch, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Ta-Chen Wu, PhD
OPDP	Aline Moukhtara, RN, MPH
OSI	Antoine El Hage, PhD
CDTL Review	John Marler, MD
OSE/DMEPA	Justine Harris, BS, RPh
OSE/DDRE	N/A
OSE/DRISK	Bob Pratt, PharmD
OMP/DMPP	Nyedra Booker, PharmD
PMHS	Donna Snyder, MD; Leyla Sahin, MD
SEALD	N/A
Other	Lana Shiu, MD (CDRH); Mark Avigan, MD (OSE); John Senior, MD (OSE); Elisa Braver, PhD (OSE)

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CDRH=Center for Devices and Radiologic Health
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development
CSS=Controlled Substance Staff

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The applicant has provided substantial evidence of effectiveness for the use of daclizumab for the treatment of patients with relapsing forms of multiple sclerosis. This conclusion is supported by evidence from two adequate and well-controlled studies (Studies 301 and 201) that evaluated the use of daclizumab at two doses. These studies were similar, differing primarily in duration and choice of control. These studies were generally of typical design and evaluated an often-used primary outcome of annualized relapse rate, comparing daclizumab to placebo in Study 201, and to Avonex, an approved therapy for relapsing forms of multiple sclerosis, in Study 301.

As noted, two doses were evaluated. Study 201 evaluated monthly doses of 150 mg and 300 mg. Similar highly statistically significant results were observed for both doses, reducing annualized relapse rate, the primary outcome, by about 54% for the low dose and 50% for the high dose, both compared to placebo. There was no suggestion of greater benefit for the high dose on various clinical measures. Accordingly, only the 150 mg dose was tested in Study 301. The effect on annualized relapse rate in that study was highly significant with a reduction of 45% against Avonex, a drug with an established effect on annualized relapse rate.

Effects on accumulation of sustained disability, measured by comparing confirmed disability progression endpoints, were not as clear. In Study 201, disability was an exploratory outcome. Nominally significant effects compared to placebo were seen for both 12- and 24-week confirmed disability progression at the 150 mg dose. Effects at the 300 mg dose were numerically superior to placebo but not nominally significant. In Study 301, disability was a secondary endpoint and was numerically superior to Avonex, a drug with an established effect on disability, but this difference (4%) was not statistically significant. Additional exploratory analyses of disability in Study 301 were nominally significant or nearly so and all numerically favored daclizumab over Avonex.

The primary effects on reduction in annualized relapse rate were supported by consistent effects on various secondary, subgroup, and sensitivity analyses.

It appears a reasonable range of doses was explored, as doses below 150 mg appeared to lack biological activity and the two upper doses of 150 mg and 300 mg had similar clinical effects.

There are significant safety concerns associated with the use of daclizumab for the treatment of relapsing forms of multiple sclerosis. The primary issues of concern are hepatic injury including autoimmune hepatitis and a constellation of immune-mediated disorders. A patient taking

300 mg died from autoimmune hepatitis, prompting changes to the protocol to improve monitoring. No additional deaths occurred following those changes. Immune-mediated disorders appear to be consistent with the activity of daclizumab and can be severe. They generally occur in small numbers individually but in aggregate are frequent, occurring in about a quarter of patients. Skin reactions are the most common. Infections can also occur, as they do with many medications for multiple sclerosis.

The severity, breadth, and character of the safety findings have prompted some members of the review team to recommend against approval. Others favor approval with strong warnings in labeling. There is general consensus that, if approved, a boxed warning is needed, a risk evaluation and mitigation strategy is required, and the drug should be reserved for use in patients who have inadequately responded to other therapies.

Given the presence of substantial evidence of effectiveness and what I judge to be an acceptable safety profile for use in patients that do not adequately respond to other therapies, the risk benefit profile of daclizumab is favorable and supports approval. Multiple sclerosis is a serious and life-threatening condition, and individual patients can have significant variability in their response to various drugs. The biological activity of daclizumab is presumed to be mediated through a mechanism not shared with other approved drugs for MS.

With regard to which dose to describe in labeling, there is no question 150 mg is the appropriate choice. A lower dose appeared inactive and a higher dose, adequately studied, conferred no additional clinical benefit.

Whether to describe the effects on disability is a reasonable question. The review team seems not to want to include them, with some clearly arguing against their inclusion and others perhaps somewhat more open to the notion. Although I understand the arguments against inclusion, I think the consistency of numerical superiority on various exploratory analyses, and the numerical, though not statistical, superiority against an active control known to have effects on disability argue for inclusion. We also recognize that effects on disability have been difficult to demonstrate and we have consistently opted to include information on disability in labeling even when it is not supported by clearly significant results, excluding it completely generally if all analyses are clearly negative. Taken in total, I believe the data support an effect of daclizumab on disability and it will be informative to the prescriber to include a description of the results for this domain. To fail to do so would, in my judgment, be misleading.

An additional issue is how to describe the indicated population. Because of the drug's toxicity, the drug should be used for patients who have had an inadequate response to other therapies. Throughout the review process, the review team has been planning to state in the indication that DAC should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. This language is identical to that used in the indication statement for alemtuzumab, a drug with significant toxicity. The sponsor has urged (b) (4) but we have not agreed to this. A reason the sponsor has cited is the

(b) (4) Experience with daclizumab prescribed and used under the conditions of the REMS may eventually decrease concerns, but at present it continues to appear reasonable to use at least two other drugs first.

We will not require pediatric studies because there is evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups.

Postmarketing requirements are needed to assess known serious risks of drug-induced liver injury, serious infections, and immune-mediated disorders, to evaluate potential risk factors for developing liver disorders and serious skin reactions, to assess a signal of a risk of breast cancer related to the use of Zinbryta , to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Zinbryta during pregnancy, and to identify an unexpected serious risk of therapeutic failure due to the presence of neutralizing anti-drug antibodies.

Postmarketing commitments are needed to evaluate the (b) (4) charge variant specification for the drug substance and the drug product, validate a non-reduced CE-SDS method and evaluation of the need for its inclusion in the drug substance and drug product specification, conduct microbial spiking studies of product intermediates, and provide additional endotoxin recovery data.

Postmarketing risk management activities will include a risk evaluation and mitigation strategy (REMS) that is necessary to ensure the benefits of the drug outweigh the risks of severe and fatal hepatic injury and serious immune-mediated disorders. The REMS will include a communication plan. The REMS will include elements to assure safe use that will ensure that health care providers who prescribe the drug are specially certified, that pharmacies that dispense the drug are specially certified, that the drug be dispensed to patients with evidence or other documentation of safe-use conditions, that each patient using the drug be subject to certain monitoring, and that each patient using the drug is enrolled in a registry. An acceptable REMS meeting these goals and including these elements has been negotiated with the sponsor.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of daclizumab for the treatment of patients with relapsing forms of multiple sclerosis.

For these reasons, I recommend approval of this application, to include the agreed-upon product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Relapsing multiple sclerosis is a condition associated with a risk of short-term disability due to relapses and a risk of gradually increasing longer-term disability due to incomplete recovery from relapses as well as from neurodegenerative changes.	Multiple sclerosis is a condition that can result in a significant loss of function over the course of a relapse as well as over the long-term course of the illness. Multiple sclerosis can be a profoundly disabling illness with onset in early adulthood.
Current Treatment Options	• There are multiple treatment options available. • Current approved therapies consistently reduce the relapse rate but may not have as consistent effects on long-term disability.	There remains a pressing need for additional treatments.
Benefit	• The evidence for a reduction in the rate of relapses is consistent. • The evidence provided suggests that there is likely a reduction in long-term disability.	The reduction in relapse rate is superior to that of a beta-interferon and the reduction in long-term disability may be comparable or superior to a beta-interferon providing an important alternative therapy.
Risk	• There is a significant risk of serious liver injury. • There is a significant risk of immune-mediated events.	Clear and informative labeling is needed, including a boxed warning.
Risk Management	• Surveillance for liver toxicity may be effective in identifying early hepatic injury. • Early detection and discontinuation of treatment may not consistently reverse the liver toxicity.	Safety concerns will require careful postmarketing risk management and the drug is most appropriately used after trials of other agents.

2. Background

Daclizumab was an approved drug, marketed as Zenapax (BLA 103749), for the prophylaxis of acute organ rejection in patients receiving renal transplants. Zenapax was to be given by intravenous injection at a dose of 1 mg/kg beginning just before transplantation and continuing for approximately two months. Marketing of Zenapax (daclizumab) was discontinued in 2009 for commercial reasons (reasons unrelated to safety or effectiveness) and the BLA was eventually revoked in February 2015.

Daclizumab, as the subject of this application, was referred to throughout the majority of development as "daclizumab high yield process (HYP)" (b) (4) At the time of submission, Zinbryta (BLA 761029) was identified for review under the Program for Enhanced Review Transparency and Communication for NME NDAs and original BLAs (known as the Program and described in the PDUFA V goals letter). Further review of the application during the review cycle has indicated that BLA 761029 may not qualify for the Program; however, consistent with FDA policy, the review of the BLA has continued to be managed under the Program for process reasons. According to CDER's review process, the signatory authority for applications managed under the Program is generally at the office level. Because this application was managed under the Program, it will be signed at the office level to be consistent with OND practice.

The Agency has decided the proper name for this product is daclizumab. We note that an alternative name, (b) (4) was not adopted by USAN (b) (4) we have considered the status of the Agency's policies on the nonproprietary naming of biological products, the previous approval by FDA of daclizumab in BLA 103749, and the current status of BLA 103749.

Regarding the Agency's current policies on the nonproprietary naming of biological products, we note that the draft guidance for industry, Nonproprietary Naming of Biological Products, has not been finalized. Consistent with FDA's good guidance practices (see 21 CFR 10.115), FDA has provided an opportunity for public comment before the guidance is finalized. Before the guidance is finalized, FDA continues to make decisions on nonproprietary names on a product-specific basis.

A key factor in FDA's current thinking regarding the necessity of adding a suffix to the proper name of certain biological products is the Agency's determination that such suffixes lower the risk of confusing different products and assist with FDA's product-specific pharmacovigilance efforts. Daclizumab was approved under BLA 103749 and that BLA has subsequently been revoked. Thus, because the biological product licensed under the current BLA (BLA 761029) will be the only daclizumab product licensed in the U.S., there appears to be no risk of product confusion at this time.

In the various reviews of the application, the terms "daclizumab" and "daclizumab HYP" are used interchangeably to refer to the subject of this application. In the remainder of this memo,

I will use the term "daclizumab" (DAC) to refer to the subject of this application. If a particular distinction is required with regard to DAC HYP or DAC (b) (4) I shall make that distinction explicitly.

DAC HYP has not previously been the subject of any marketing application. It is intended to be used as for the treatment of relapsing forms of multiple sclerosis (MS).

Though numerous medications have been approved for relapsing forms of MS, there can be considerable variability in individual responses to these different medications and patients with MS may have inadequate control of their disease despite treatment with available therapy.

Although the precise mechanism of action of DAC is unknown, DAC is a humanized monoclonal antibody which binds to CD25, a subunit of the interleukin-2 (IL-2) receptor, and it is theorized that DAC may exert its effects via effects on this receptor. This activity appears to be distinct from the varied biological activities of the other drugs approved for the treatment of MS.

The applicant is Biogen. Biogen is an established company in the development of MS drugs. Sponsorship of DAC throughout development has involved several companies as commercial arrangements resulted in changes in multiple changes of ownership. The application was originally submitted in February 2015 by Abbvie, but Biogen participated in the pre-submission discussion in light of plans to assume ownership of the application in May 2015. The Division was involved throughout the development of DAC, and Dr. Rodichok has a detailed presentation in his review of the regulatory history and interactions with those sponsors. Selected important issues of discussion during development included adequate exploration of nonclinical findings, endpoint selection in clinical studies, methods of statistical analysis, and the presentation of safety information.

This application is intended to establish the effectiveness of DAC based primarily on the results of 2 randomized double-blind studies: a 2 year active-controlled study, Study 301; and a 1 year placebo-controlled study, Study 201. The sponsor submitted Study 301 for special protocol assessment and, after revising the protocol following initial review, received a special protocol assessment agreement letter from the Division. A pre-BLA meeting held on October 8, 2014, led to agreement with the sponsor that data from Studies 301 and 201 could potentially provide substantial evidence of effectiveness.

I will briefly discuss the major findings of the review team.

3. Product Quality

I concur with the conclusions reached by the chemistry and device reviewers regarding the acceptability of the manufacturing of the drug product and drug substance and of the prefilled syringe (b) (4) Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months at 2-8ºC. The manufacturing review team has negotiated with the sponsor a postmarketing requirement concerning the detection of

neutralizing antibodies and postmarketing commitments concerning evaluation of the (b) (4) charge variant specification for the drug substance and the drug product, validation of a non-reduced CE-SDS method and evaluation of the need for its inclusion in the drug substance and drug product specification, microbial spiking studies of product intermediates, and additional endotoxin recovery data. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Dr. Carbone reviewed this submission and found it unacceptable. He does not recommend approval. He bases his recommendation on nonclinical findings of microglial aggregates in monkey throughout the brain and spinal cord that were not accompanied by signs of axonal degeneration or myelin loss. Dermal findings of skin lesions were also present. These findings were generally reversible over recovery periods of 4 to 12 weeks. Dr. Carbone notes that the biological significance of the microglial aggregates is unclear. Dr. Carbone notes several concerning aspects of this finding. First, it cannot be clinically monitored. Next, any effect of this finding on existing pathology in MS patients is unknown. Finally, he calculates a 9-fold safety margin for the microglial aggregates. Because of these issues involving microglial aggregates, in particular the safety margin, along with the availability of alternative therapy, Dr. Carbone recommends against approval.

Dr. Lois Freed also considers these issues in her supervisory memo. With regard to the finding of microglia aggregates, Dr. Freed makes several points that, while agreeing that Dr. Carbone's concern in this area is reasonable, reduce the degree of that concern. First, the severity of the finding was always minimal, even at maximum dosing. Next, there was no evidence, even in specially conducted focused studies that we requested, of aggregate-associated neuronal degeneration, axonal fragmentation, or demyelination. Additionally, the nature of the aggregates did not appear to be characteristic of direct neurotoxicity. Finally, she calculates that a 7-fold safety margin exists for the presence of a single microglial aggregate in the low dose group in the chronic toxicity studies. Overall, she concludes that, for these reasons, the observed microglial aggregates are not of sufficient concern to preclude approval and the nonclinical data are therefore adequate to support approval, with appropriate labeling, if the clinical risk benefit assessment supports approval. She also notes that no postmarketing assessments are needed.

Overall, after carefully considering Dr. Carbone's reasoning, it appears to me that Dr. Freed's stance that it is appropriate to have a somewhat lower degree of concern than that espoused by Dr. Carbone is reasonable. I concur with Dr. Freed that the observed microglial aggregates are not of sufficient concern to preclude approval and that there are no outstanding nonclinical issues that preclude approval.

5. Clinical Pharmacology

I concur with the conclusions reached by Dr. Wu that there are no outstanding clinical pharmacology issues that preclude approval. His review discusses the usual pharmacokinetic (PK) and pharmacodynamic (PD) considerations. Selected findings include:

- Exposure-response analyses show a flat relationship for efficacy and safety in the range of exposures associated with 150 mg and 300 mg dosing, supporting the proposed dose of 150 mg. Pharmacodynamic markers suggested a lack of biological effect with 75 mg dosing.

- Elimination half-life is approximately 3 weeks.

- Hepatic metabolism and renal elimination are not expected and no dosing adjustments are required for renal impairment.

- Neutralizing antibodies, occurring in about 3-8% of patients, increased clearance by about 19% but this had no discernable impact on clinical effect.

- Dosing adjustments in the presence of concomitant medications that are substrates of CYP isozymes are not required.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

As discussed by Dr. Ling, Dr. Rodichok, and Dr. Marler, 2 studies provide the primary data intended to support efficacy, Studies 301 and 201, respectively. I will briefly discuss these studies and refer to the team's reviews for additional detailed discussion.

As Dr. Marler and other members of the review team note, these studies were parallel-group, fixed-dose, randomized, double-blind, controlled studies that enrolled patients with relapsing MS. Study 301 was active-controlled using the approved drug for relapsing MS Avonex (interferon beta-1a) as a comparator and was conducted using a double-dummy approach to blinding. Study 201 was placebo-controlled, with 150 mg and 300 mg doses. Enrollment criteria are summarized in the various reviews. Patients were adults with relapsing MS. Similar populations were enrolled in both studies. Study 301 included patients from North America; Study 201 did not. Patients from the United States and Canada constituted approximately 13% of the total population of Study 301.

Eligible subjects were enrolled and treated for 2 years in Study 301 and 1 year in Study 201. Doses of DAC evaluated in the studies ranged from 150 mg to 300 mg, given by subcutaneous injection every 4 weeks. Study 301 evaluated a monthly dose of 150 mg. Study 201, which was the earlier study, evaluated monthly doses of 150 mg and 300 mg, and finding no advantage with the higher dose, led to the choice of 150 mg for Study 301.

More patients discontinued from Study 301 than Study 201, with a retention rate of patients in Study 301 of about 75-80% and in Study 201 of about 90%. Discontinuation was generally due to adverse events. Patients in the various arms of the studies were well-matched on demographic characteristics. There were more patients in Study 301 than in Study 201 who had taken a prior MS therapy.

The primary outcome measure in both studies was the annualized relapse rate (ARR) over the time of the study. The ARR was based on confirmed relapses.

Dr. Ling describes the following secondary outcomes for Study 301, in order of hierarchical analysis:

1. number of new or newly enlarging T2 hyperintense lesions on brain MRI over 96 weeks;
2. proportion of subjects with confirmed disability progression;
3. proportion of subjects who are relapse-free;
4. proportion of subjects with a ≥7.5-point worsening from baseline in the MSIS-29 Physical Impact score at 96 weeks.

Dr. Ling describes the following secondary outcomes for Study 201, in order of hierarchical analysis:

1. the number of new Gd+ lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24;
2. the number of new or newly enlarging T2 hyperintense lesions at Week 52;
3. the proportion of subjects relapsed between baseline and Week 52;
4. change in MSIS-29 physical score at Week 52 compared to baseline.

Dr. Ling notes that disability progression was a tertiary endpoint in Study 201.

The following modified table from page 25 of Dr. Rodichok's review summarizes the characteristics of these 2 studies:

Trial Identity	Trial Design	Regimen/ schedule/ route	Primary Study Endpoint	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
Study 201 (SELECT)	RCT; 2 doses vs. placebo	150 mg or 300 mg q4W	ARR	52 weeks	621	Relapsing forms of MS	78 sites in 9 countries – all OUS
Study 301	RCT; 1 dose vs. IFN β 1a	150mg SC q4W vs 30 µg IM qW	ARR	96 weeks	1841	Relapsing forms of MS	245 sites in 28 countries

The following table taken from page 19 of Dr. Marler's review summarizes the primary outcome findings along with additional data on number of patients without relapse (a secondary outcome) for Studies 301 and 201.

Relapses: Primary Outcome For Trials 201 and 301						
			DAC-HYP 300mg	DAC-HYP 150mg	Avonex	Placebo
Trial 301	N (randomized)	1841		919	922	
	ARR			0.216	0.393	
		% Reduction		45%		
		p-value		<.0001		
	% Relapse Free			72%	57%	
		Absolute Difference[24]		15%		
		NNT[24]		6.6		
Trial 201	N	600	203	201		196
	ARR		0.230	0.211		0.458
		% Reduction	50%	54%		
		p-value	.0002	<.0001		
	% Relapse Free		80%	81%		64%
		Absolute Difference[2]	15%	16%		
		NNT[24]	6.6	6.25		

There was a highly significant effect on ARR in both studies, with a somewhat smaller effect size seen against the active control (45% reduction) than against the placebo (54% reduction), but both effects are substantial. For a secondary endpoint closely related to the primary outcome, more DAC patients than control were free of relapse in both studies. There was no additional benefit seen with the high dose in Study 201.
Dr. Marler presents the results of the secondary outcomes for Studies 301 and 201 in these tables from page 19 of his review:

Trial 301 Secondary Outcomes				
Hierarchy of Outcomes	Avonex	DAC-HYP 150mg	p	Relative Risk
1. new or newly enlarging T2 at 96 weeks	9.44	4.21	<.0001	
2. Percent with progression of disability for 12 weeks at 144 weeks	20.3%	16.2%	.1575[25]	.798
3. Proportion of subjects free from relapse at 96 weeks	58%	73%	ns	
4. Proportion at least 7.5-points worse on MSIS-29 at 96 weeks	23%	19%	ns	

Trial 201 Secondary Outcomes					
Hierarchy of Outcomes	Placebo	DAC-HYP		p-value	
		150 mg	300 mg	150 mg	300 mg
1. mean new Gd-enhancing lesions in 5 MRI scans up to24 weeks[26]	5.7	3.1	1.4	<.0001	<.0001
2. new or newly-enlarging T2 hyperintense lesions at Week 52	8.2	3.4	2.1	<.0001	<.0001
3. proportion with relapses between baseline and Week 52	35%	19%	20%	<.0001	<.0001
4. mean change in MSIS-29[27] from baseline at Week 52	3.0	-1.0	1.4	.0008(ns)[28]	0.1284

There was a highly significant effect on MRI assessments in both studies.

In Study 301, disability progression trended numerically in favor of DAC compared to active control, but was not statistically significant. As Dr. Ling notes, because the difference between treatments in the primary analysis of 12-week confirmed disability progression was not statistically significant, the testing of lower-ranked secondary endpoints, including proportion of patients relapse free, was stopped within the closed testing procedure. Accordingly, Dr. Marler does not provide p-values for lower-ranked secondary outcomes. Dr. Ling provides the nominal p-value for the final two secondary outcomes, $p<0.0001$ and $p=0.0176$, respectively. The numerical results of all secondary outcomes favored DAC. It seems hard to ignore the relapse free outcome and it will be included in labeling.

In Study 201, there was a highly significant effect on proportion of patients relapsed favoring DAC compared to placebo. The final secondary outcome was not significant for either dose because the closed testing procedure assessed the 300 mg dose group first, and it was not significant.

Although a pre-specified effect on disability was numerically superior but not statistically significant in Study 301, as noted above, additional exploratory assessments are presented by Dr. Ling to provide additional context to this result. Two pre-specified sensitivity analyses (recognizing, again, that the initial analysis did not reach statistical significance) that examined tentative, but unconfirmed, reports of disability progression both favored DAC. The first assumed that all tentative progressions were confirmed. The second used a model to generate a probability that a tentative progression would be confirmed based on various covariates. The nominal p-values for these analyses were 0.0157 and 0.0469. Dr. Ling conducted her own additional sensitivity analysis to examine these tentative progressions based on reasonable assumptions about the likelihood of confirmation of a tentative progression (leading to "confirmation" of 50% of the tentative progressions) and Dr. Ling reports a marginal trend towards significance with a p-value of 0.0556.

Dr. Marler presents the following table on page 21 of his review summarizing additional explorations of disability in Study 301.

Selected Trial 301 Tertiary Outcomes

Hierarchy of Outcomes	Avonex	DAC-HYP 150mg	p
24-week disability progression at week 144 (%)	18.3%	12.7%	.0332
24-week disability progression at week 96 (%)[30]	12.1%	9.2%	
EDSS change from baseline to week 96	-0.01	-0.02	.3742

Although these findings are exploratory and p-values represent nominal calculations, numerical trends are seen that favor DAC over Avonex for all findings.

Effects on disability were exploratory assessments in Study 201. The following table from page 20 of Dr. Marler's review summarizes those findings.

Selected Trial 201 Tertiary Outcomes					
Hierarchy of Outcomes	Placebo	DAC-HYP		p-value	
		150 mg	300 mg	150 mg	300 mg
12-week disability progression at week 52 (%)	13.2%	5.9%	7.8%	.0211	.0905
24-week disability progression at week 52 (%)[29]	11.1%	2.6%	6.8%	.0037	.1487
EDSS change from baseline to week 52	0.09 (± 0.71)	-0.08 (± 0.52)	0.05 ± 0.61)	0.0102	0.4874

Although these findings are exploratory and p-values represent nominal calculations, numerical trends are seen that favor DAC over placebo for all findings.

Various sensitivity analyses of the primary and secondary outcomes were consistent and supportive. Dr. Ling and Dr. Rodichok note that subgroup analyses by demographic characteristics were relatively consistent with the primary findings, with some suggestion of relatively larger treatment effect in European patients, in patients with mild baseline disease, and in patients not previously treated with interferon beta. Overall, additional subgroup explorations reported by Dr. Ling and Dr. Rodichok did not suggest substantial differences from the primary and major secondary findings.

Overall, Dr. Ling, Dr. Rodichok, and Dr. Marler all agree that effectiveness of DAC has been demonstrated and recommend approval, with some differences of opinion on the strength of supportive data. All agree that there is strong evidence supporting the effectiveness of the 150 mg dose on relapse rate and that there is no evidence suggesting additional benefit with the 300 mg dose. All agree that there is strong evidence supporting effects on MRI measures. Dr. Ling feels there is a marginal trend towards significance of an effect on disability. Dr. Rodichok feels that it is likely that an effect of DAC on disability is similar to that of Avonex as seen in Study 301 and that the data from Study 201 are too limited in number and duration to allow for a meaningful conclusion, but that the numerical findings do provide some support for an effect on disability attributable to DAC. Dr. Marler does not feel that a clear effect on disability has been demonstrated, noting that subjectivity of assessments in the setting of possible unblinding due to side effects combined with small numbers of events and the occurrence of dropout leading to missing data all make the interpretation of the various exploratory analyses of disability difficult. He does not, however, feel these concerns undermine the credibility of the primary results of the trial. In sum, Dr. Marler feels that there is clear evidence that DAC reduces relapse rate and that arguments suggesting an effect on disability are plausible but unreliable.

8. Safety

As discussed in the review of Dr. Villalba, there are significant safety issues associated with the use of DAC for the treatment of relapsing MS. In addition to her detailed discussion of safety findings, Dr. Sally Jo Yasuda provides a thorough secondary review of the safety

findings and Dr. Marler summarizes the safety findings and issues in his memo. I will briefly consider the major issues they have discussed.

The size of the safety database was adequate. Safety assessments were deemed generally adequate by the review team. Dr. Villalba and Dr. Yasuda note that the overall presentation of data for safety analyses in the application was of poor quality and results of these analyses may underestimate toxicity associated with use of DAC. There was considerable exposure to the proposed dose of 150 mg. Similarly, there was substantial exposure in MS patients. A large portion of the exposure comes from the randomized, double-blind, controlled studies of relapsing MS discussed above.

There were 10 deaths reported in the application, with 5 occurring in DAC-treated patients (4 at 150 mg and 1 at 300 mg) and 5 occurring in Avonex-treated patients. Although the numbers were balanced, 2 deaths in DAC patients appeared clearly related to drug while none of the Avonex deaths were clearly drug-related. The death associated with DAC 300 mg was clearly related to drug. This patient had an autoimmune hepatitis with subsequent liver failure leading to death after resuming treatment with DAC following a treatment interruption of 6 months. The other death clearly related to DAC was a case of severe eczema complicated by development of bacteremia, psoas abscess, and ischemic colitis, which were the immediate causes of death. The review team points out that the infectious contribution to the patient's death was likely related to the cutaneous reactions, which is reasonable. I have reviewed the other deaths, and I agree with the team that the remaining 3 cases in DAC-treated patients and 5 in Avonex-treated patients are of uncertain relationship to drug exposure.

As Dr. Marler points out, there were 3% more serious adverse events (SAEs) in DAC-treated patients than in patients exposed to Avonex in Study 301, and if serious adverse events of MS relapse were excluded the difference was 6%. In Study 201 using placebo as a comparator there was no significant excess of serious adverse events in DAC-treated patients. Dr. Villalba, Dr. Yasuda, and Dr. Marler have discussed safety concerns of interest thoroughly in their comprehensive and summary reviews. Dr. Villalba has included a concise summary of the primary safety findings in her summary framework at the beginning of her review, which have been further summarized with additional commentary by Dr. Yasuda and Dr. Marler. Main findings include:

Drug-Induced Liver Injury (DILI)
Serious DILI, including the death described above, occurred in 20 DAC subjects (0.9%). SAEs of DILI (including liver failure) and transaminase elevations occurred more frequently in DAC than in placebo or interferon beta-1a in controlled trials. Seven DAC subjects had autoimmune hepatitis and 4 subjects had transaminase and bilirubin elevations in the Hy's law range (including 2 of the patients with autoimmune hepatitis) for which a role for DAC cannot be ruled out. Onset of DILI is unpredictable, it occurs despite monitoring, it can be fatal, and risk factors to predict patients who are susceptible are not yet identified. Serious DILI occurred despite stringent monitoring and a requirement to review liver laboratory values prior to the next dose. With regard to the DILI-associated death, this occurred after an interruption in DAC. Prior to restarting DAC 300 mg, the patient was treated with another hepatotoxic agent. After restarting, dosing continued despite elevated liver enzymes. Following the

patient's death, modifications to the protocol were instituted to increase monitoring and mandate assessment of laboratory values prior to monthly dosing. Following these changes, there were no additional fatalities. Dr. Avigan provided a consultative review of the liver findings and recommended regular assessment and monitoring in order to attempt to reduce serious outcomes, but he recognized that such a strategy would not be able to fully eliminate that risk. Dr. Senior opted to provide an additional consideration of the issue, and expressed concern regarding the utility of such monitoring, as it will not eliminate the risk and there may be issues with compliance.

Autoimmune and Immune-Mediated Events

DAC associated immune-mediated adverse events affecting most organ systems occurred in approximately 30% of DAC-treated subjects overall. In addition to autoimmune hepatitis and skin conditions, including eczema and other dermatitis (discussed separately), a variety of conditions occurred infrequently, including psoriatic conditions (2%), enteropathy (1.2%), immune-mediated hepatitis (0.53%), sarcoidosis (0.3%), vasculitis (0.3%), celiac disease (0.2%), glomerulonephritis in 2 subjects (< 0.1%), and autoimmune hemolytic anemia in 3 subjects (0.1%). Non-infectious colitis-related events occurred in 1.5% of DAC-treated subjects (of which 0.3% were SAEs) and none of the interferon beta-1a-treated subjects in Study 301. Multiple events in a single patient could occur. Three subjects had a rash with involvement of other organs or blood count abnormalities, such as eosinophilia, and at least 5 others had multiorgan failure that may have been immune-mediated. Note that some of these cases are referred to in some of the reviews as cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) but Dr. Yasuda has reconsidered these cases and determined that they do not fulfill the criteria for DRESS. Dr. Rosenberg provided a review of the autoimmune findings in the development program and concludes that DAC is related to their occurrence. She also made recommendations for additional information that could be explored in an attempt to gain insight into the predictability of autoimmune adverse events.

Dermatologic Reactions

Dermatologic reactions occurred more frequently in DAC-treated patients than in those exposed to control in the controlled trials; overall, they occurred in 40% of DAC-treated subjects. The events ranged from mild to severe and life-threatening reactions, some requiring treatment with systemic steroids, and some that required months to resolve after discontinuing DAC.

Acute Hypersensitivity

Acute hypersensitivity included angioedema, anaphylaxis, and serious urticaria. Acute hypersensitivity events occurred throughout the time period of treatment with DAC. In Study 301, these events were about twice as common with DAC as with Avonex.

Infections

There were more infections in DAC-treated groups than the comparator groups in controlled trials, and they occurred in 4-5% of all DAC-treated patients. Serious infections occurred at a rate three times that with Avonex or placebo treatment. Serious infections included urinary tract infection, pneumonia, appendicitis, cellulitis, infectious enterocolitis, and viral infections.

Depression and Suicide
In controlled trials, depression-related events occurred in 10% of DAC-treated patients compared to 8% of Avonex-treated patients and in 7% of DAC-treated patients compared to 2% of patients taking placebo. In controlled trials, serious events related to depression, suicidal ideation, or suicide attempt occurred in 0.4% of DAC-treated patients, in 0.7% of Avonex-treated patients, and none in placebo.

Seizures
Though seizures are known to occur in MS, seizure SAEs occurred in 0.7% of DAC and 0.2% of Avonex subjects in Study 301, and Avonex has a warning in labeling regarding seizures.

Malignancies
The rate of breast cancer in the DAC-treated cohort may exceed the reported background rate in the general population. There were 8 cases in women and 1 case in a man. Dr. Yasuda notes a rate of breast cancer in females in the total DAC-exposed database of 185 to 212/100,000 compared to an expected background rate ranging from 43 to 126/100,000.

Lymphadenopathy
Lymphadenopathy was more common in the DAC group than in the Avonex group in Study 301 (6% vs 1%). Lymphadenopathy occurred in 2% in the DAC group compared with 1% in the placebo group in Study 201. Lymphadenopathy may be associated with other disease.

Sarcoidosis
There are 9 diagnosed cases of sarcoidosis and 4 other suggestive cases. Although there may be a plausible link to DAC, the background rate cited by the sponsor suggests that the identified cases do not exceed that rate. A consultative review provided by Dr. Braver concludes that the analysis provided by the sponsor was inconclusive.

Renal Effects
Although there was no overall imbalance in renal findings, there were two cases of glomerulonephritis in DAC patients. The review team notes that these may be related to DAC.

Dr. Yasuda and Dr. Marler have provided summaries of Dr. Villalba's detailed presentation of common adverse event, laboratory, and vital sign data, and I refer to their summaries for further discussion.

There is no foreign marketing experience with this dosing regimen.

Dr. Pratt has provided a review of the sponsor's proposed risk evaluation and mitigation strategy (REMS). Dr. Pratt, along with other members of the Division of Risk Management and of the review team, met numerous times to discuss the proposed REMS and decide if a REMS was necessary to ensure that the benefits of the drug outweigh the risks. On March 8, 2016, DAC was presented at a meeting of the REMS Oversight Committee (ROC). The ROC recommended that REMS with elements to assure safe use, including a REMS registry, should be required for the approval of daclizumab. After extensive discussion, we have determined that a REMS is necessary to ensure that the benefits of the drug outweigh the risks of severe

and fatal hepatic injury and serious immune-mediated disorders. The REMS will include a communication plan. The REMS will include elements to assure safe use that will ensure that health care providers who prescribe the drug are specially certified, that pharmacies that dispense the drug are specially certified, that the drug is dispensed to patients with evidence or other documentation of safe-use conditions, that each patient using the drug be subject to specified monitoring, and that each patient using the drug is enrolled in a registry. An acceptable REMS meeting these goals and including these elements has been negotiated with the sponsor.

Overall, Dr. Villalba does not recommend approval because of safety concerns. She notes that there are other approved drugs for MS. Dr. Senior makes a similar recommendation. Dr. Villalba does note that if approved, she recommends strong warnings, including a boxed warning, for DILI and immune-mediated events, a REMS in order to help mitigate some of the risks associated with its use, and notes that the product should not be for first line use. Dr. Avigan makes similar recommendations concerning the need for monitoring. Dr. Rosenberg recommends that the application either not be approved because of safety concerns or that it be restricted to an acceptable subset of patients. Dr. Yasuda, in her supervisory memo, notes, in consideration of Dr. Villalba's recommendation, along with those of Dr. Senior and Dr. Rosenberg, that a recommendation regarding approvability can only be made based on a consideration of benefit and risk. Dr. Yasuda notes that the safety reviews provide assessments of the risk, as well as recommendations for labeling and strategies to mitigate the risk if it is determined that the benefits outweigh the risk such that DAC would be approved. Dr. Yasuda agrees with Dr. Villalba's recommendations for strongly worded labeling including a boxed warning, a REMS, and avoidance of first line use. Dr. Villalba, Dr. Avigan, Dr. Rosenberg, and Dr. Yasuda have all made recommendations for postmarketing requirements and activities to further characterize and mitigate the risks associated with DAC. Dr. Marler recommends approval with appropriate labeling.

9. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because the safety profile, although it includes serious risks, is not clearly worse than other drugs to treat MS and daclizumab represents a presumably novel mechanism of action. The safety profile is acceptable for the treatment of relapsing forms of multiple sclerosis. The clinical trial design is similar to that of trials of previously approved drugs for the treatment of relapsing forms of multiple sclerosis, so that effectiveness is not in doubt. The drug was compared to an established effective agent, Avonex, and was markedly superior. It should be notee that at a previous advisory committee meeting concerning significant risks associated with a new drug for relapsing forms of multiple sclerosis, the committee and community clearly voiced the opinion that such risks are not an obstacle to approval in this disease, that new and varied therapies are needed and valued by the community, and that even severe risks should be labeled appropriately but should not preclude approval given the severity of the disease and the varied clinical response and circumstances of individual patients. We have heard similar sentiments from the MS community in our general interactions with MS patients and

organizations. The drug will, however, be recommended in labeling for use in patients who have had an inadequate response to 2 or more drugs approved for the treatment of MS.

10. Pediatrics

We are waiving the pediatric study requirement for this application because there is evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Postmarketing

As noted above, the members of the review team agree that a REMS is required for this application. I agree.

Postmarketing requirements and commitments, and related issues, do not include a requirement for pediatric studies, as noted above.

Postmarketing requirements are needed to assess known serious risks of drug-induced liver injury, serious infections, and immune-mediated disorders, to evaluate potential risk factors for developing liver disorders and serious skin reactions, to assess a signal of a risk of breast cancer related to the use of Zinbryta , to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Zinbryta during pregnancy, and to identify an unexpected serious risk of therapeutic failure due to the presence of neutralizing anti-drug antibodies.

Postmarketing commitments are needed to evaluate the (b) (4) charge variant specification for the drug substance and the drug product, validate a non-reduced CE-SDS method and evaluation of the need for its inclusion in the drug substance and drug product specification, conduct microbial spiking studies of product intermediates, and provide additional endotoxin recovery data.

14. Decision/Action/Risk Benefit Assessment

The applicant has provided substantial evidence of effectiveness for the use of daclizumab for the treatment of patients with relapsing forms of multiple sclerosis. This conclusion is supported by evidence from two adequate and well-controlled studies (Studies 301 and 201) that evaluated the use of daclizumab at two doses. These studies were similar, differing primarily in duration and choice of control. These studies were generally of typical design and evaluated an often-used primary outcome of annualized relapse rate, comparing daclizumab to placebo in Study 201, and to Avonex, an approved therapy for relapsing forms of multiple sclerosis, in Study 301.

As noted, two doses were evaluated. Study 201 evaluated monthly doses of 150 mg and 300 mg. Similar highly statistically significant results were observed for both doses, reducing annualized relapse rate, the primary outcome, by about 54% for the low dose and 50% for the high dose, both compared to placebo. There was no suggestion of greater benefit for the high dose on various clinical measures. Accordingly, only the 150 mg dose was tested in Study 301. The effect on annualized relapse rate in that study was highly significant with a reduction of 45% against Avonex, a drug with an established effect on annualized relapse rate.

Effects on accumulation of sustained disability, measured by comparing confirmed disability progression endpoints, were not as clear. In Study 201, disability was an exploratory outcome. Nominally significant effects compared to placebo were seen for both 12- and 24-week confirmed disability progression at the 150 mg dose. Effects at the 300 mg dose were numerically superior to placebo but not nominally significant. In Study 301, disability was a secondary endpoint and was numerically superior to Avonex, a drug with an established effect on disability, but this difference (4%) was not statistically significant. Additional exploratory analyses of disability in Study 301 were nominally significant or nearly so and all numerically favored daclizumab over Avonex.

The primary effects on reduction in annualized relapse rate were supported by consistent effects on various secondary, subgroup, and sensitivity analyses.

It appears a reasonable range of doses was explored, as doses below 150 mg appeared to lack biological activity and the two upper doses of 150 mg and 300 mg had similar clinical effects.

There are significant safety concerns associated with the use of daclizumab for the treatment of relapsing forms of multiple sclerosis. The primary issues of concern are hepatic injury including autoimmune hepatitis and a constellation of immune-mediated disorders. A patient taking 300 mg died from autoimmune hepatitis, prompting changes to the protocol to improve monitoring. No additional deaths occurred following those changes. Immune-mediated disorders appear to be consistent with the activity of daclizumab and can be severe. They generally occur in small numbers individually but in aggregate are frequent, occurring in about a quarter of patients. Skin reactions are the most common. Infections can also occur, as they do with many medications for multiple sclerosis.

The severity, breadth, and character of the safety findings have prompted some members of the review team to recommend against approval. Others favor approval with strong warnings in labeling. There is general consensus that, if approved, a boxed warning is needed, a risk evaluation and mitigation strategy is required, and the drug should be reserved for use in patients who have inadequately responded to other therapies.

Given the presence of substantial evidence of effectiveness and what I judge to be an acceptable safety profile for use in patients that do not adequately respond to other therapies, the risk benefit profile of daclizumab is favorable and supports approval. Multiple sclerosis is a serious and life-threatening condition, and individual patients can have significant variability in their response to various drugs. The biological activity of daclizumab is presumed to be mediated through a mechanism not shared with other approved drugs for MS.

With regard to which dose to describe in labeling, there is no question 150 mg is the appropriate choice. A lower dose appeared inactive and a higher dose, adequately studied, conferred no additional clinical benefit.

Whether to describe the effects on disability is a reasonable question. The review team seems not to want to include them, with some clearly arguing against their inclusion and others perhaps somewhat more open to the notion. Although I understand the arguments against inclusion, I think the consistency of numerical superiority on various exploratory analyses, and the numerical, though not statistical, superiority against an active control known to have effects on disability argue for inclusion. We also recognize that effects on disability have been difficult to demonstrate and we have consistently opted to include information on disability in labeling even when it is not supported by clearly significant results, excluding it completely generally if all analyses are clearly negative. Taken in total, I believe the data support an effect of daclizumab on disability and it will be informative to the prescriber to include a description of the results for this domain. To fail to do so would, in my judgment, be misleading.

An additional issue is how to describe the indicated population. Because of the drug's toxicity, the drug should be used for patients who have had an inadequate response to other therapies. Throughout the review process, the review team has been planning to state in the indication that DAC should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. This language is identical to that used in the indication statement for alemtuzumab, a drug with significant toxicity. The sponsor has urged (b) (4) (b) (4) but we have not agreed to this. (b) (4) (b) (4) Experience with daclizumab prescribed and used under the conditions of the REMS may eventually decrease concerns, but at present it continues to appear reasonable to use at least two other drugs first.

We will not require pediatric studies because there is evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups.

Postmarketing requirements are needed to assess known serious risks of drug-induced liver injury, serious infections, and immune-mediated disorders, to evaluate potential risk factors for developing liver disorders and serious skin reactions, to assess a signal of a risk of breast cancer related to the use of Zinbryta , to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Zinbryta during pregnancy, and to identify an unexpected serious risk of therapeutic failure due to the presence of neutralizing anti-drug antibodies.

Postmarketing commitments are needed to evaluate the (b) (4) charge variant specification for the drug substance and the drug product, validate a non-reduced CE-SDS method and evaluation of the need for its inclusion in the drug substance and drug product specification, conduct microbial spiking studies of product intermediates, and provide additional endotoxin recovery data.

Postmarketing risk management activities will include a risk evaluation and mitigation strategy (REMS) that is necessary to ensure the benefits of the drug outweigh the risks of severe and fatal hepatic injury and serious immune-mediated disorders. The REMS will include a communication plan. The REMS will include elements to assure safe use that will ensure that health care providers who prescribe the drug are specially certified, that pharmacies that dispense the drug are specially certified, that the drug be dispensed to patients with evidence or other documentation of safe-use conditions, that each patient using the drug be subject to certain monitoring, and that each patient using the drug is enrolled in a registry. An acceptable REMS meeting these goals and including these elements has been negotiated with the sponsor.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of daclizumab for the treatment of patients with relapsing forms of multiple sclerosis.

For these reasons, I recommend approval of this application, to include the agreed-upon product labeling.

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/s/

WILLIAM H Dunn
05/27/2016