CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 6, 2016
From	John R. Marler, MD
Subject	Cross-Discipline Team Leader Review
Application Number	BLA 761029
Applicant	Biogen
Date of Submission	February 27, 2015
PDUFA Goal Date	May 27, 2016
Name Proprietary/ Non-Proprietary	Zinbryta (daclizumab)
Dosage form	150 mg in a pre-filled syringe for subcutaneous injection every 4 weeks
Applicant's Proposed Indication	Relapsing forms of multiple sclerosis
Recommended Regulatory Action	Approval
Recommended Indication	Daclizumab is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of daclizumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Relapsing multiple sclerosis is a chronic and potentially disabling brain disease of unknown etiology characterized by intermittent episodes of focal neurological deficit and scattered lesions of demyelination in the brain. In some patients, there is a gradual accumulation of disability over decades. Severe disability early in the course of the disease is not common. The relapse symptoms themselves may be disabling for short periods, usually 30-days or less. Despite the slow course of the disease, some patients with the disease express high tolerance for the possibility of serious adverse effects of any drug that may reduce relapse rates or disability over the longer term of the disease. There are eleven different FDA-approved drugs for MS. All have frequent or serious adverse effects. The unmet need for relapsing MS is a drug or drug combination that prevents long-term disability better than available treatments and does so with fewer adverse effects.

The primary benefit of treatment with daclizumab is a reduction in relapse rates. The 1841-patient Trial 301, performed under a Special Protocol Assessment, showed a statistically significant 45% reduction in relapse rate *compared to Avonex*.[1] The proportion of patients without any relapses for **two years** in Trial 301 differed by 15%, favoring daclizumab over Avonex. Number needed to treat in order to prevent relapses in one patient for two years would be approximately 6. The statistical confidence interval may underestimate the uncertainty about the actual relapse rates because of the presence of common unblinding side effects and a 30% dropout rate. The 600-patient Trial 201 showed a 54% reduction in relapse rates *compared to placebo*. The number of patients without any relapses for **one year** in Trial 201 differed by 16%. Uncertainty in Trial 201 is due to significant design issues, the potential for unblinding, and the one-year duration of the trial.

It is less certain that patients can expect daclizumab to reduce the number of episodes of disability progression lasting 12 weeks or more. As defined in the statistical analysis plans, there was no statistically significant change in the incidence of disability progression lasting 12 weeks in either Trial 301 or Trial 201.[2] The point estimates for the proportion of patients who experienced disability progression taking daclizumab are less than control by 4% over two years and 7% over 1 year in Trial 301 and Trial 201, respectively. These differences are small when compared to the potential bias introduced by the study design and execution of the

[1] This review refers to the specific product, Avonex, rather than interferon β-1a, because there are three products approved for this drug substance: Avonex, Rebif, and Plegridy. The dose is specific for each product. Avonex is for IM and the others for SQ administration.

[2] There were trends showing a reduction in both trials. Trial 201 had nominally significant results but these were not statistically significant due to multiplicity adjustment and inclusion of disability as an exploratory measure.

trials. There was no clinically significant overall change from baseline in the mean disability scores over the duration of the two trials despite the reduction in of the number of episodes of disability progression in either trial in all treatment groups.[3]

In contrast to the uncertainty of the effect of daclizumab on disability, it is clear that daclizumab exposes all patients to the risk of serious adverse events. *Safety reviews* identified major and potentially life-threatening safety events[4] that occurred more often with daclizumab than placebo or Avonex. They included drug-induced liver injury (DILI), serious immune-mediated reactions, infections, seizures, malignancies, depression, and suicidality. These potentially disabling events were more frequent with daclizumab than either placebo or Avonex. There is no way to predict which patients will experience these adverse events. They occurred throughout the course of therapy and some occurred after discontinuation of daclizumab. Some of these events resolved months after discontinuing daclizumab and some required invasive procedures for diagnosis and treatment with additional immunosuppressive medications. The clinical safety reviewers and consultants concluded that significant benefit would be required to offset the risks of daclizumab.

Because the sponsors did not include a global measure of disability that would integrate risks and benefits, there is no direct measure of global benefit. Because bias was poorly controlled, the point estimates for the clinical outcomes are likely inaccurate in favor daclizumab. One can construct plausible arguments that Trial 301 shows that the effect of daclizumab on disability progression is non-inferior or even superior to that of Avonex. To do so one must assume that that bias was well controlled, dropout was uninformed, that unblinded treating physicians accurately reported subjective clinical outcomes, that corrections for multiplicity adjustment can be overlooked, the statistical model accounts for bias, or that a failed superiority outcome can be interpreted as noninferiority. These assumptions may be misleading, particularly in contrast to the certainty of the serious safety concerns.

One possible benefit is that daclizumab may offer a reduced relapse rate to patients who experience relapses despite taking another approved drug because it has a different mechanism of action and there is uncertainty about the disease and drug mechanisms. There is no direct evidence of this possible benefit.

In conclusion, daclizumab reduces the relapse rate compared to Avonex but at increased risk of serious life-changing adverse effects and without substantial evidence of a meaningful reduction in episodes of increased disability lasting 12-weeks or longer. Approval is recommended with labeling that describes these serious risks and uncertain benefits.

[3] Table 5, page 20, and Table 6, page 20.

[4] Excluding relapses reported as serious adverse events. See Table 15 and Table 16, below

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Relapsing multiple sclerosis is a chronic and potentially disabling brain disease of unknown etiology characterized by intermittent episodes of focal neurological deficit and scattered lesions of demyelination in the brain. • The usual age of onset of RMS is 20 to 50 years. Symptoms include relapsing episodes of diminished sensory or motor function that can be disabling and usually resolve within one month. Over several years, many, but not all, MS patients experience some degree of persistent disability that may gradually worsen over years. The course varies widely. Some patients have a relatively benign course; others become severely disabled after only a few years. There are no reliable predictors of long-term outcome. • Reducing relapse rates is a meaningful benefit in itself: a reduced number of potentially disabling episodes that usually resolve within a month. Many patients and physicians anticipate an early reduction in relapses will also prevent or slow the development of serious disability over the decades of the disease. Substantial evidence of this anticipated benefit is lacking. • Despite the slow course of the disease, some patients with the disease express high tolerance for short-term adverse effects of a drug that may reduce relapse rates and long-term disability.	The usually slow and intermittent course of RMS and the lack good predictors of long-term outcome make it difficult to determine if long-term benefits of treatment balance adverse effects.
Current Treatment Options	• Eleven different drugs are FDA-approved to treat multiple sclerosis. Four of the 11 are interferon-β1(a or b) products. All of the drugs reduce relapse rates. The mechanism of action is unknown for all of these approved drugs. • Evidence of an effect on disability progression during the two-	The unmet need for relapsing MS is a drug or drug combination that prevents long-term disability better than available treatments and does so with fewer adverse

	year exposure in most RMS trials is weaker than the evidence of a reduction in relapse rate. The evidence in RMS drug labels for a reduction in disability progression shows smaller effect sizes and lacks confirmation in a second trial for some drugs.[5] • The major uncertainties are due to the subjectivity of the clinical outcomes, relapse and disability progression, different operational definitions of the outcomes, and the fact that most of the drugs approved for MS have frequent characteristic side effects that make effective blinding difficult. In some trials, dropout rates are high. Bias may explain some portion of the effects observed in the trials. • MRI findings may be more objective but there is no clear link between clinical outcomes and MRI changes. • One of the interferons, Rebif, has demonstrated superiority to another interferon (Avonex[6]) in reducing the proportion of relapse free patients at 2 years. • Because of serious safety concerns, the alemtuzumab label restricts use to patients who have not responded adequately to two or more other approved therapies. • Tysabri is associated with risk of PML, a potentially fatal opportunistic infection of the brain. The risk of PML is approximately 0.2% per year of treatment. PML occured at a lower incidence in patients taking Gilenya and Tecfidera. • Labels for 10 of 11 FDA-approved MS drugs report disability progression outcomes.[7] In some of these labels, all the	effects. Comparing outcomes in trials of different drugs is potentially misleading because of different populations, trial duration, and operational definitions of the two clinical outcomes: relapse and disability progression. None of the currently approved drugs stands out from the rest.

[5] See Appendix, Table 25 and Table 26
[6] Avonex is interferon β-1a, *the active comparator* in the major Trial 301 that confirms daclizumab reduces relapse rate.
[7] Appendix, Table 25

	disability outcomes are not statistically significant but all except the Copaxone and Novantrone labels contain at least one trial that showed a statistically significant effect (p-value less than 0.05) for a disability progression outcome at two years.	
Benefit	• Two controlled trials of daclizumab show a reduction of annual relapse rate with daclizumab by 45% compared to Avonex (interferon beta-1a) in one trial and 54% compared to placebo in the other. [8] The populations had similar baseline disease severity.[9] As with other MS drugs, the evidence that daclizumab reduces disability is less certain than the evidence of a reduction in relapse rate.[10] In neither of the two trials was there a statistically significant effect on 12-week disability progression.[11] Point estimates of the proportion of patients who experienced disability progression differed from control by 4% to 7% of patients. In particular, there is uncertainty that daclizumab is better than the interferons in reducing disability progression. This uncertainty is due to the small effect size (4-7% of patients), the lack of a statistically significant effect in the larger active control trial, reliance on post-hoc and exploratory analyses, unplanned midstream changes in the sample size and primary outcome in one trial, 30% dropout rate in one trial, and evidence that blinding was not effective. In addition, the difference between mean baseline and end-of-trial disability measured by EDSS was	The effect of daclizumab on relapses is consistent in both clinical trials. Some might question whether the 201 trial was adequate and well controlled because of midstream major changes in the primary outcome measure and sample size. The magnitude of a reduction in disability progression did not stand out in relation to other approved drugs. By the pre-specified analyses, neither trial showed a statistically significant benefit for disability. Exploratory disability outcome analyses showed nominally significant results. Some of the effect on relapses and disability is likely due to bias. For relapses, the relative contribution of bias to the difference in relapse rate may be relatively smaller than that for disability

[8] Table 2, page 13
[9] Table 1, below, page 14
[10] Table 3, page 15.
[11] Table 5, page 16, and Table 6, page 17

	clinically insignificant (less than 0.02 EDSS points in Trial 301 at two years and less than 0.10 EDSS points at one year in Trial 201).[12]	progression because the absolute number of patients who had a relapse differed by 16% while the number with disability progression differed by 4% and 7%. There is insufficient evidence to conclude that daclizumab significantly reduces disability progression sustained for 12 weeks.
Risk	• Treatment with daclizumab is associated with two deaths in clinical studies. Excluding MS relapses, in the 1841-patient Trial 301 there were 6% more patients with serious adverse events in the daclizumab treatment group than in the Avonex control group.[13] Safety reviews identified major and potentially life-threatening safety events that included drug-induced liver injury (DILI), serious immune-mediated reactions, infections, seizures, malignancies, depression, and suicidality. There is no way to predict which patients will experience these adverse events. They occurred throughout the course of therapy and some occurred after discontinuation of daclizumab. Some of these events resolved months after discontinuing daclizumab and some required invasive procedures for diagnosis and treatment with additional immunosuppressive medications. After the death due to hepatitis, protocols required monthly liver function tests. There is uncertainty about the completeness of safety data	The serious adverse events that the sponsor reported are greater for daclizumab than either placebo or Avonex. Incomplete AE reporting may lead to an underestimate of the toxicity of daclizumab The excess serious adverse events in daclizumab-treated patients in Trial 301 are not offset by a corresponding reductions in relapses reported as serious adverse events.

[12] Prior to randomization the average yearly EDSS progression was 0.361 and 0.338 EDSS points per year. Table 1, page 16.

[13] See Table 15. The rates were lower over one-year in Trial 201.

	reporting because of errors and omissions identified during the safety review. • The observation in nonclinical studies of microglial brain aggregates that are not associated with any apparent effects presents a potential risk to patients. However, there was no apparent effect noted in the safety data from clinical studies.	
Risk Management	• The Safety Review Team and their consultants recommend monthly laboratory testing. The review team, in concert with the REMS oversight committee agrees that approval of daclizumab mandates a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) because of the requirement for monthly laboratory testing prior to each dose.	

2. Background

ZIMBRYTA (daclizumab) for subcutaneous injections from prefilled syringes has a different route of administration that the daclizumab marketed from 1997 to 2009 as Zenapax for intravenous infusion to prevent rejection after organ transplant.[14] Daclizumab is a humanized monoclonal antibodies that binds to the α-subunit of the IL2 receptor on T-cells. Biogen proposes to market daclizumab for treatment of relapsing forms of multiple sclerosis.

Relapsing multiple sclerosis (RMS) is a chronic progressive brain disorder characterized by episodes of neurological dysfunction, relapses, which generally occur at a rate of once every two years and usually last less than 30 days. Most commonly, *relapses* are episodes of weakness or numbness in an arm or leg, pain and loss of vision in one eye, unsteady walking, double vision, difficulty speaking, or dizziness. Early in the disease course, the relapse symptoms resolve leaving minimal or no disability. The clinical symptoms and rate of worsening are widely variable. In some longitudinal studies, the progression of irreversible disability occurs independently from relapses as if they are two separate aspects of the disease.[15] Generally, the age that symptoms first appear is 20-50 years. Two-thirds of patients are women. Over several years, many, but not all, MS patients experience some degree of persistent disability. Among those who do become disabled, the mean time from first symptoms is 11.4 years until disability becomes significant but leaving the patient self-sufficient and up and about some 12 hours a day and able to walk without aid or rest for 500 meters. The average time is 23.1 years before there is a need for a cane or crutch despite the ability to walk 100 meters.[15] MS shortens lifetimes by about 5 years. Patients and patient advocates at FDA advisory committee meetings state that some MS patients, particularly those with active disease, have a very high tolerance for adverse effects because of their concerns about long-term disability.

Eleven different drugs are FDA-approved to prevent relapses in RMS.[16] Five of the 11 are interferon β-1(a or b) products. All of the drugs reduce relapse rates. One of the

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[14] The approved dose of Zenapax is 1mg/kg IV every 14 days for a total of 5 doses. The proposed dose for daclizumab is 150mg SC every 4 weeks for an indefinite period.

[15] Christian Confavreux, M.D., Sandra Vukusic, M.D., Thibault Moreau, M.D., And Patrice Adeleine, M.D., Relapses And Progression of Disability In Multiple Sclerosis, NEJM, November 16, 2000, No. 20, Volume 343, pp. 1430-8.

[16] Betaseron, Avonex, Copaxone, Rebif, Tysabri, Gilenya, Aubagio, Tecfidera, Plegridy, Lemtrada, and Novantrone. Extavia is Betaseron under another name and Glatopa is a generic form of Copaxone.

interferons, Rebif, has demonstrated superiority to another interferon β-1, Avonex, for reducing the proportion of relapse free patients at 2 years. In general, evidence of an effect on disability progression during the two-year exposure in most RMS trials is weaker than the evidence of a reduction in relapse rate. The evidence in RMS drug labels for a reduction in disability progression shows smaller effect sizes and lacks confirmation in a second trial for some drugs.[17]

Because of serious safety concerns, the alemtuzumab label restricts use to patients who have not responded adequately to two or more other approved therapies. Tysabri is associated with risk of PML, a potentially fatal opportunistic infection of the brain. The risk of PML is approximately 0.2% per year of treatment. PML has occurred in a smaller proportion of patients under treatment with fingolimod and dimethyl fumarate.

The etiology of MS relapses and disability progression is unknown and may differ among individuals. Daclizumab is different from the other approved MS drugs because it targets the IL-2 receptor. No other approved MS drug targets the IL-2 receptor.

The Division of Neurology Products issued a Special Protocol Agreement for Trial 301 with the annual rate of relapses as the primary outcome.

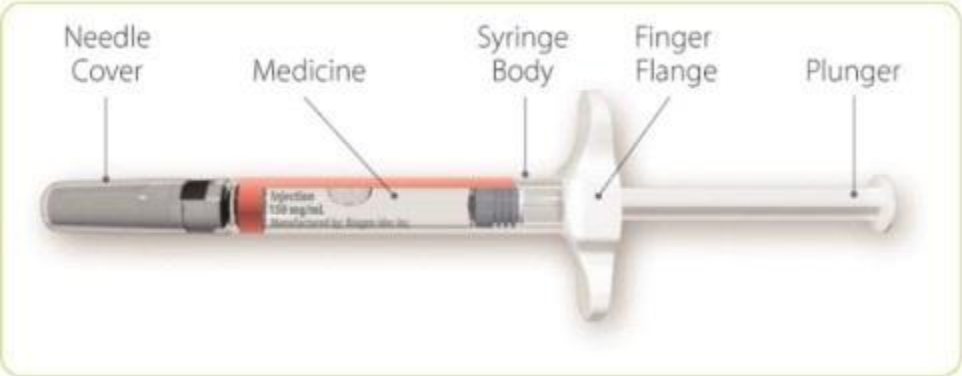
3. Product Quality

The 11-member quality assessment team[18] recommends approval. They find that the data in the application support the conclusion that the manufacture of Zinbryta (daclizumab) is well controlled and leads to a product that is pure and potent. The team recommends 7 post-marketing commitments (PMRs). One PMR calls for development of assays to detect neutralizing antibodies that are tolerant to the presence of daclizumab at all levels likely to be present in patients on treatment. The other 6 PMRs are to validate assays, conduct product quality studies, and re-evaluate specifications. Figure 1 depicts the pre-filled syringe to be used by patients for subcutaneous injection.

[17] Table 26, Appendix, page 48

[18] Chen Sun (Drug Substance, Drug Product, Immunogenicity); Bo Chi (Microbiology Drug Substance); Colleen Thomas (Microbiology Drug Product; Wayne Seifert (Facility); Anita Brown (Regulatory Business Process Manager); Joel Welch (Application Technical Lead, Drug Substance and Drug Product Team Leader); Patricia Hughes, (Microbiology Team Lead); Peter Qiu (Facilities Team Lead); Juhong Liu (OBP Branch Chief)

Figure 1 Daclizumab 150mg Prefilled Syringe



Christopher J. Brown, P.E., performed the CDRH review of the device. He recommended the pre-filled syringe for daclizumab is approvable from the perspective of the applicable Quality System Requirements. He did not find deficiencies in the documentation review of the application for compliance with the Quality System Requirements. Inspections were conducted and deemed acceptable.

4. Nonclinical Pharmacology/Toxicology

David Carbone, Ph.D., performed the nonclinical pharmacology and toxicology review. The most significant toxicities identified in nonclinical studies were red, raised, and patchy areas of the skin and scattered microglial aggregates throughout the brain and spinal cord. Skin and brain toxicities generally resolved within 12 weeks. Because the proposed 150mg dose is not within the safety margin established for microglial aggregates, because there is no way to monitor the presence of the aggregates clinically, and because alternative therapies for relapsing forms are available, Dr. Carbone recommends against approval of daclizumab.

In her secondary review, Lois Freed, Supervisory Pharmacologist, determined that the microglial aggregates are not of sufficient concern to preclude approval, particularly if the clinical team concludes that there is sufficient evidence of efficacy in humans to warrant approval in light of the serious toxicities already demonstrated in humans.

Microglial aggregates occurred after a single 200 mg/kg subcutaneous dose in nonclinical studies. See Figure 2. Mononuclear cell infiltration and hemosiderin deposits (indicators of hemorrhage) accompanied some of the microglial aggregates. There was no evidence of axonal degeneration or myelin loss. In 9-month studies, the highest dose that did not produce microglial aggregates was 10 mg/kg administered biweekly. No symptoms correlated with the presence of the aggregates in nonclinical studies.

Figure 2 Microglial Aggregate. The glial cells have more condensed, have less round nuclei and are intermixed with inflammatory cells. Animal 4007, H&E, 40X, Slide 1

Nonclinical toxicology studies found skin toxicity consistent with that observed in clinical trials. However, it is unknown whether microglial aggregates are similarly replicated in humans, because this finding cannot be monitored in a clinical setting. Concern over the microglial aggregates is due to the unknown effect of this abnormality on any existing neuroinflammation in the intended patient population. Based on steady state exposures in monkeys at the NOAEL and humans receiving the proposed clinical dose, the safety margin for the microglial aggregates is approximately 9-fold.[19] Given this inadequate safety margin for the microglial aggregates and the availability of alternate therapy for relapsing forms of MS, daclizumab, Dr. Carbone does not recommend approval.

Skin toxicity only occurred with repeat doses. There was no dose tested that had no skin toxicity.

5. Clinical Pharmacology

The clinical pharmacology review team primary reviewer was Ta-Chen Wu, Ph.D. His team leader was Angela Men, M.D., Ph.D. Pharmacometrics reviewers were Xiaofeng Wang, Ph.D. and Kevin Krudys, Ph.D. Pharmacogenomics reviewers were Hobart Rogers Pharm.D, Ph.D. and Christian Grimstein Ph.D. The team found the application acceptable if the sponsor accepts appropriate changes to their proposed label.

[19] A safety margin of 10-fold the no adverse effect level (NOAEL) dose from nonclinical studies is the standard requirement for safety.

General clinical pharmacology: absorption, food effects, bioavailability

The median time to maximum concentration (T_{max}) after SC administration is 1 week. The absolute bioavailability of subcutaneous daclizumab 150mg is 90%. After the fourth monthly dose, daclizumab 150 mg reaches a steady-state serum level approximately 2.5-fold that of a single dose. In MS patients taking 150 mg SC doses of daclizumab once a month, the estimated steady-state volume of distribution of daclizumab is approximately 6.34 liters. This distribution volume suggests daclizumab distributes to the vascular and interstitial spaces.

Pathway of elimination, including metabolism, half-life, and excretion

Daclizumab has an elimination half-life ($t_{1/2}$) of approximately 3 weeks. Elimination occurs via proteolysis, target-mediated elimination, and nonspecific endocytosis. As a protein, it will undergo catabolism to peptides and amino acids in the same manner as endogenous IgG. Hence, daclizumab is not expected to undergo renal or hepatic elimination. The clearance of daclizumab is 0.212 liters per day. Clearance in patients with neutralizing antibodies was approximately 19% higher.

Factors potentially affecting elimination: age, gender, hepatic impairment, and renal impairment.

Age, weight, and sex do not affect exposure to daclizumab or its pharmacodynamics to an extent that would require dosage adjustment. The sponsor observed similar pharmacokinetic parameters in Japanese and Caucasian subjects. The clinical pharmacology team could not rule out race-specific differences in pharmacokinetics for other races because there were so few subjects in these subgroups. The label will recommend against daclizumab use in pediatric patients due to the risk of hepatic injury, autoimmune and other immune-mediated conditions, skin reactions, and malignancies.

Renal impairment does not require a dose adjustment because the kidneys are not a significant route of elimination. Neither is the liver. However, abnormal liver function is a contraindication to starting treatment with daclizumab.

Drug-drug interactions

Multiple doses of daclizumab 150 mg SC every 4 weeks in MS patients had no significant effects on the pharmacokinetics of probe substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A in MS patients. Therefore, medications that are substrates of these CYP enzymes do not require dosage adjustment when given concomitantly with daclizumab.

Immunogenicity

Neutralizing antibodies (Nab) increased daclizumab clearance by 19% but there was no discernible affect of immunogenicity on the efficacy, safety, or pharmacodynamics. Antidrug antibodies and NAbs (transient or persistent) had no apparent effect on relapse rate, adverse events, serious adverse events, cutaneous events, infections, or liver function tests. Product Quality review recommends development of an assay that is tolerant to the presence of the drug. See 3-Product Quality, above, and 13-Postmarketing Recommendations, below.

Thorough QT study or other QT assessment.

The sponsor did not study the effect of daclizumab on QT or QTc because, as a monoclonal antibody, daclizumab has a low likelihood of direct ion channel interactions.

Hepatotoxic drugs

Trial 301 excluded patients currently taking **valproic acid, carbamazepine, lamotrigine, or phenytoin** unless they had been taking only one of these medications at a stable dose for at least 6 consecutive months prior to randomization. Trial 301 also excluded patients who were taking **isoniazid, propylthiouracil, or nimesulide** at the time of randomization.[20]

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Larry Rodichok performed the primary clinical review for this BLA application. He concludes that <u>there is convincing evidence that daclizumab reduces the relapse rate</u> in patients with relapsing MS in comparison to Avonex but that <u>there is *not* convincing evidence that daclizumab has a clinically meaningful beneficial effect on disability</u> compared to Avonex.

The statistical reviewer, Xiang Ling, Ph.D., concludes that the data overall provided adequate evidence to support the efficacy of daclizumab 150 mg as treatment of subjects with relapsing MS.

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[20] Trial 301 Clinical Study Report page 49 of 112.

In his clinical review, Dr. Rodichok performed his own analysis of important outcomes in the 301 and 201 Trials. He found no significant discrepancies between his own analyses and those of the sponsor. The statistical reviewer, Xiang Ling, Ph.D., confirmed the accuracy sponsor's analyses and compliance with the statistical analysis plan that the sponsor submitted just prior to locking the study database.

The remainder of this review describes pertinent features of the trial designs, presents trial results as reported by the sponsor and then focuses on the uncertainties about the effect of daclizumab on disability. In general, this review agrees with Dr. Rodichok that daclizumab reduces relapse rate but may not have a clinically meaningful effect on disability. This review also includes an Appendix with tabular summaries of the disability and relapse outcomes presented in labels of other FDA-approved MS drugs corroborated by similar tables constructed by Dr. Rodichok.[21]

Trial Design

Two trials evaluated the efficacy of daclizumab for RMS: Trial 301**,** a *two-year* 1841-subject active-controlled trial, and trial 201, a *one-year* 621-subject exploratory placebo-controlled trial. The DNP issued an SPA Agreement Letter for the Trial 301 protocol after performing a Special Protocol Assessment (SPA). The sponsor did not request an SPA agreement for the Trial 201 protocol.

Trial 301, an 1841-patient randomized 1:1 double-blind trial, compared 150mg of daclizumab by subcutaneous injection every 4 weeks to 30 mcg of Avonex interferon β-1a by intramuscular injection once per week. The Trial 301 protocol scheduled clinic visits every 12 weeks for up to 144 weeks or until 96 weeks after randomization of the last patient. The sponsor chose the 150mg dose because Trial 201 had shown no additional benefit for a 300mg dose despite increased adverse events. The primary outcome was annualized relapse rate (ARR). Clinicians administered the daclizumab injections from vials, not from the prefilled syringes the applicant will market.

Trial 201, a 52-week, double-blind, controlled trial, compared 150 mg and 300 mg subcutaneous doses of daclizumab to placebo in 621 patients with relapsing multiple sclerosis randomized 1:1:1. The protocol divided the 52-week trial into two parts: a 24-week placebo controlled trial (Part 1) followed by a 28-week placebo controlled part that allowed patients to choose to add a β-interferon (Part 2) to the study treatment. The primary outcome was annualized relapse rate (ARR).

[21] Table 25, Table 26, and Table 27 beginning on page 47.

The main differences between the designs for Trials 201 and 301 were that Trial 301 exposed patients for two-plus years compared to one year, had four times as many patients per treatment group, and used an active comparator rather than a placebo control.

Both trials use the same definitions of relapses and 12-week disability progression. Scheduled disability score examinations (EDSS) occurred every 3 months.

Uncertainties and significant issues introduced by the trial design are discussed below on page 25.

Results

Dr. Ling agrees with the applicant that for the primary efficacy endpoint there was a 54% reduction compared to placebo in Trial 201 and a 45% reduction compared to Avonex in Trial 301 (p-value less than 0.0001 for both trials). She considered the evidence for a reduction in relapse rate to be robust because of supporting sensitivity analyses and subgroup analyses. In addition, she states that daclizumab treatment resulted in a "numerical" (not statistically significant) slowing of disability progression as measured by EDSS.

Study Population

Baseline characteristics for Trial 201 and 301 are in Table 1 for comparison. Despite differences in the inclusion criteria related to the number of prior relapses and the number of MRI lesions at baseline, the two trials appear to have recruited populations with similar baseline EDSS, enhancing lesions at baseline, and relapses in the year prior to randomization. The most prominent difference appears to be in the use of MS therapy prior to randomization. Compared to Trial 201, a higher proportion of patients in Trial 301 had taken approved MS treatments prior to randomization. See Table 1, below.

Table 1 Trial 301 Summary of Baseline Characteristics for Trial 201 and 301

Trial 301 and 201 Summary Table of Baseline Characteristics[22]					
	Trial 301		Trial 201		
Baseline Characteristic	IFN β-1a	Daclizumab	Placebo	Daclizumab 150mg	Daclizumab 300mg
N	922	919	204	208	209
Age	36.2	36.4	36.6	35.3	35.2
Female	68%	68%	63%	67%	64%
Mean Year Since MS Onset	6.92	6.96	7.4	7.3	7.2
Relapses in past year	1.58	1.53	1.3	1.4	1.3
Prior MS therapy[23]	41%	41%	24%	25%	23%
Enhancing lesions at baseline	2.26	1.98	2.0	2.1	1.4
EDSS Mean	2.54	2.48	2.7	2.8	2.7
EDSS Max	6	5.5	5	5	5
EDSS Median	2.5	2	2.5	3.0	2.5
EDSS progression per year[24]	0.361	0.287	0.338	0.411	0.347

Study Completion

In Trial 301, 71% of the subjects completed at least 96 weeks of their assigned treatment. For all subjects, the mean time on treatment was 100.54 weeks for the IFN β-1a group and 102.04 weeks for the daclizumab group.[25]

In In Trial 201, 96% of the subjects completed 52 weeks of their assigned treatment. For all subjects, the mean time on treatment was 46.14 weeks for the IFN β-1a group, 45.78 weeks for the daclizumab 150mg group, and 45.99 weeks for the daclizumab 300 mg group.

Primary outcome

The table below summarizes the sponsor's primary clinical efficacy results. Both trials show a reduction in the annualized relapse rate (ARR) in patients with relapsing MS.

[22] Trial 301 study report page 127-156 of 3937

[23] Prior therapy with Avonex, Betaseron or Extavia, Copaxone, Rebif or other immunomodulatory treatment. Trial 301 study report page 153 of 3937. Trial 201 Study Report page 349 of 1641.

[24] Calculated by CDTL: (mean EDSS at baseline)/(mean years since onset of MS)

[25] Trial 301 study report page 159 of 3937 and Trial 201 study report page 349 or 3937.

Table 2 Annualized Relapse Rate: Primary Outcome for Trials 201 and 301

Relapses: Primary Outcome For Trials 201 and 301						
			Daclizumab 300mg	Daclizumab 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[26]		15%		
		NNT[26]		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[26]	6.6	6.25		

Secondary Outcomes

The evidence for the effect of daclizumab on disability comes from secondary and exploratory outcomes of the two trials.

In *Study 301*, there was a 4% difference in the proportion of patients with 12-week confirmed disability progression at 144 weeks (p=0.1575, not statistically significant; 20% Avonex vs 16% daclizumab). The sponsor's results for pre-specified secondary outcomes for *Trial 301* are in Table 3, below. No p-value is given for the 3rd and 4th secondary outcomes because the hierarchical sequential test procedure stopped further statistical testing when the p-value for progression of disability (2nd secondary outcome) exceeded 0.05. The sponsor reports that the hazard ratio for 12-week disability progression is 0.84 for daclizumab compared to Avonex; the confidence interval on the hazard ratio is 0.66 to 1.07.

In her review, Dr. Ling noted that there are a substantial number of subjects with "tentative" disability progression events unconfirmed by a second evaluation. She states that sensitivity analyses based on reasonable assumptions regarding the unconfirmed tentative disability progressions suggest a treatment effect with marginal statistical significance in Trial 301.

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[26] CDTL calculation based on sponsor's results.

Table 3 Trial 301 Secondary Outcomes

Trial 301 Secondary Outcomes				
Hierarchy of Outcomes	Avonex	Daclizumab 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[27]	.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	

The sponsor's results for secondary outcomes for *Trial 201* are in Table 4, below. Disability progression was not a primary or secondary outcome in this trial. The p-value less than 0.05% for the 4th secondary outcome, Multiple Sclerosis Impact Scale (MSIS), is not considered significant because the hierarchical sequential test procedure stopped when the p-value for the 300mg dose was 0.1284 (greater than 0.05).

Table 4 Trial 201 Secondary Outcomes

Trial 201 Secondary Outcomes					
Hierarchy of Outcomes	Placebo	Daclizumab		p-value	
		150 mg	300 mg	150 mg	300 mg
1. mean new Gd-enhancing lesions in 5 MRI scans up to24 weeks[28]	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[29] from baseline at Week 52	3.0	-1.0	1.4	.0008(ns)[30]	0.1284

[27] The sponsor performed alternate analysis for disability progression that they had not pre-specified and produced results that were nominally statistically significant. They also performed an exploratory analysis for SAD at 6 months and reported a nominally significant result. Despite the plausibility of any argument the sponsor presents to discount the pre-specified outcome, multiple analyses, particularly those that are not pre-specified, can be misleading by chance alone. In light of the likely bias due to ineffective blinding and the play of chance in post-hoc analysis, it would be misleading to suggest on the label that evidence shows that daclizumab is superior to Avonex with regard to sustained disability progression. This is particularly important because of the known serious safety concerns: it would be misleading to decide that weak results potentially overstating the effects on disability can balance known safety concerns.

[28] protocol-defined subset of subjects (the MRI-intensive population) consisting of the first 307 subjects enrolled in the Trial 201.

Selected Exploratory Outcomes

Even though the Trial 201 secondary outcome hierarchical analysis would have stopped because the daclizumab 300mg dose p-value was more than 0.05, the sponsor and Dr. Rodichok cite evidence with nominal statistical significance from some of the exploratory analyses of daclizumab on disability. In Study 201, disability progression was an exploratory endpoint. The result showed a 57% reduction in 12-week confirmed disability progression (nominal p=0.0211) in the treatment group compared to placebo. The difference in proportion of patients between the two arms was 7% (NNT=14) at one year compared to 4% (NNT=25) at two years in Trial 301. The study report included p-values for these outcomes even though the sequential hierarchical analysis would have stopped before the exploratory analyses. The average change from baseline EDSS score at week 52 was neither clinically nor statistically significant. See Table 5.

Table 5 Selected Trial 201 Exploratory Outcomes

Selected Trial 201 Exploratory Outcomes					
Hierarchy of Outcomes	Placebo	Daclizumab		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 (%)[31]	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

Exploratory outcomes for Trial 301 included proportion of 24-week disability progression events and overall change from baseline for the EDSS. See Table 6, below. Multiple exploratory MRI outcome measures showed a statistically significant effect. See Table 7.

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[29] MSIS-29: Multiple Sclerosis Impact Scale, a patient reported outcome measure

[30] Page 53 of 254, SAP for Trial 201: "a sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons with the first comparison (the daclizumab 300 mg group versus placebo) and the second comparison (the daclizumab 150 mg group versus placebo). Secondary endpoints have been rank prioritized in the order shown in Section 16. 1.2 in the protocol. A closed testing procedure will be used for the secondary endpoints such that if statistical significance is not achieved from an endpoint for a comparison, all endpoint(s) of a lower rank for that comparison will not be considered statistically significant."

[31] An "exploratory" post-hoc hypothesis not in the original SAP or protocol.

Table 6 Selected Trial 301 Exploratory Outcomes

Selected Trial 301 Exploratory Outcomes			
Hierarchy of Outcomes	Avonex	Daclizumab 150mg	p
24-week disability progression at week 144 (%)	18.3%	12.7%	.0332
24-week disability progression at week 96 (%)[32]	12.1%	9.2%	
EDSS change from baseline to week 96	-0.01	-0.02	.3742

The changes in EDSS over one year in Trial 201 and over two years in Trial 301 suggest no statistically significant change in EDSS attributable to daclizumab compared to placebo or Avonex. As noted above, issues related to study design add further uncertainty to the determination whether daclizumab has a clinically meaningful effect on disability. See the discussion of uncertainties below, on page 25.

Table 7 Trial 301 Exploratory MRI Outcomes

Trial 301 Exploratory MRI Outcomes
Brain atrophy
Number of new or newly enlarging T2 hyperintense lesions over 24 weeks
Number of new T1 lesions over 24 and 96 weeks
Number of Gd+ lesions at Weeks 24, and 96
Volume of T1 hypointense lesions at Weeks 24 and 96
Volume of T2 hyperintense lesions at Weeks 24 and 96
Volume of new or newly enlarging T2 lesions
Proportion of subjects who are free of disease activity over 96 weeks

ARR in Patient Subgroups

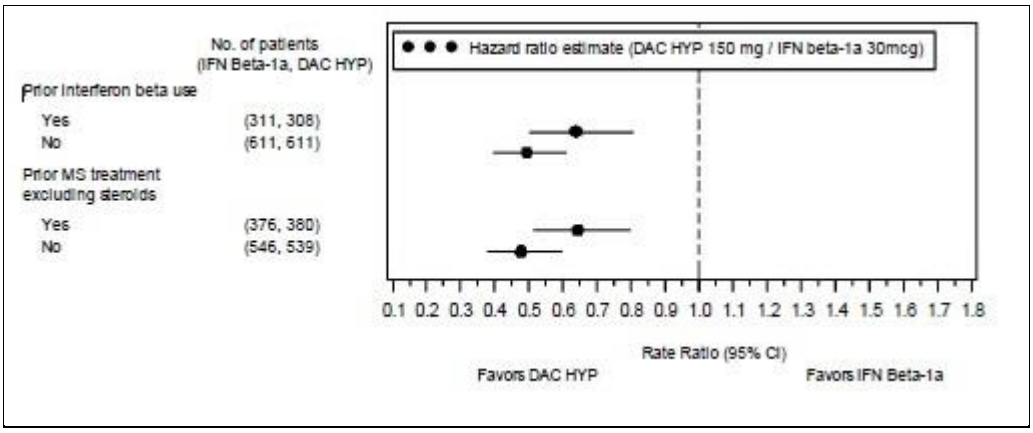
For all subgroups, the point estimates of the annualized relapse rate in both trials favors daclizumab. The confidence interval of the rate ratio was below 1.0 for all subgroups except those patients with a baseline EDSS score 3.5 or greater and patients in North America. In Table 53 of his review, Dr. Rodichok shows a treatment response in all racial subgroups for Trial 301; 90% of trial subjects were white. The greatest reduction in ARR occurred in the white subpopulation; the least reduction in the Asian subpopulation.

[32] Sponsor post-hoc analysis included by CTDL for comparison with trials for other FDA-approved MS products which have most often been based on 2 years of observation.

Neither Trial 201 nor Trial 301 directly addressed whether daclizumab worked in patients who failed prior MS therapies. Patients treated with other MS drugs prior to randomization had to have stopped the drug from 30 days to one year before entering the trial. Patients were not included if they did not have evidence of recent disease activity.

Dr. Rodichok found that daclizumab-treated patients had a higher rate of relapse if they had taken interferon β before randomization in Trial 301 and had a greater reduction in ARR with daclizumab compared to Avonex if they had no prior therapy (Figure 3, below). In Trial 201, patients with no prior MS treatment showed the greatest differences in the response to treatment. The sponsor analyzed relapse rate and proportion with relapse at one year for Trial 301 and 201, respectively. See the sponsor's data in Table 8 and Table 9, below.

Figure 3 Trial 301 Forest Plot ARR With and Without Prior MS Treatment[33]



[33] Adapted from Trial 301 CSR, Figure 10, page 230 of 3937.

Table 8 Trial 301 Relapse Outcome for Subgroups With and Without Prior MS Treatment

Trial 301 Relapse Outcome For Subgroups With and Without Prior MS Therapy					
Trial 301	Prior immunomodulatory therapy for MS excluding steroids[34]	% of Patients in Trial	Avonex	Daclizumab 150	Reduction in ARR
			Annualized Relapse Rate[35]		
	Prior MS Therapy	41%	0.401	0.258	36%
	No Prior MS Therapy	59%	0.277	0.132	52%

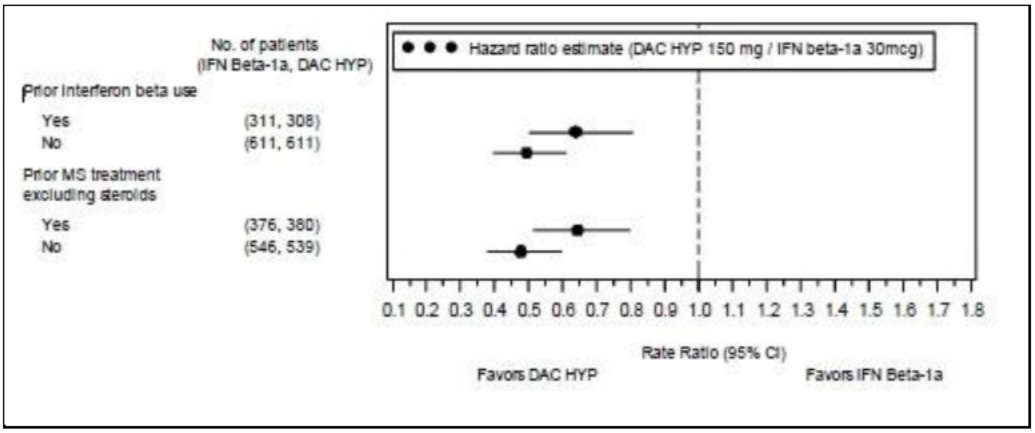
In Trial 201, a difference from Trial 301 is apparent. Those with no prior MS treatments in Trial 201 had a 57% reduction in the incidence of one or more relapses over one year when treated with daclizumab compared to placebo. Compared to 57%, the risk reduction was 6% in those patients who had received prior treatment with Copaxone or one of the interferons. Note that "No Prior Treatment" for Trial 201 included all treatments other than steroids as opposed to just treatments approved at the time of the trial as for Trial 301 in Table 8.

[34] Avonex, Betaseron or Extavia, Copaxone, Rebif, or other unknown MS therapy. Excludes 12 patients who took natalizumab, 1 who took fingolimod, and 2 who took teriflunomide.
[35] Table 150, Trial 301 Clinical Study Report, page 878 of 3937

Table 9 Trial 201 Patients with Relapse at 52 Weeks in Subjects With and Without MS Therapy Prior to Randomization

Trial 201 Proportion with Relapse at 52 Weeks For Subgroups With and Without Prior MS Therapy						
	Prior immunomodulatory therapy for MS excluding steroids[36]	% of Patients in Trial	Avonex	Daclizumab 150	Daclizumab 300	Relative Risk Reduction for DAC 150
Trial 201		% of pts	Proportion with Relapse in One Year[37]			
	Prior MS Therapy	76%	31%	29%	26%	6%
	No Prior MS Therapy	24%	38%	16%	18%	57%

Figure 4 Trial 301 Forest Plot ARR With and Without Prior MS Treatment[38]



[36] All MS therapies other than steroids
[37] Table 87, Trial 201 Clinical Study Report, page 349 of 1641
[38] Adapted from Trial 301 CSR, Figure 10, page 230 of 3937.

Significant Review Issues in Clinical Trial Design, Conduct, or Analysis

In the clinical review, Dr. Rodichok identifies a number of uncertainties related to the design, conduct, and analysis of the two clinical trials.

Effectiveness of Blinding

There is some evidence that blinding was not effective in Trial 301. Most MS trials, including Trial 201 and 301, use blinded evaluators for the EDSS scale to reduce observer bias. In these trials, however, patients and treating physicians who may have been unblinded by side effects made the significant decisions required to determine if a relapse event occurs.

From Dr. Rodichok's review: " *A relapse was defined as any new or recurrent neurologic symptoms that correlate with an "objective" neurologic deficit on examination by the examining neurologist or technician. A minimum increment in neurologic deficit was not required. An assessment of EDSS, MSFC and VFT*[39] *was included in the assessments by the examining neurologist/technician if the event was referred by the treating neurologist*."

Although described by the applicant as based on "objective" deficits, relapses are subjective events reported by patients and screened by potentially unblinded treating physicians to select the subset of patients who receive formal neurological examinations performed by blinded examiners on potentially unblinded subjects. Before examination by blinded examiners, the protocol requires clinical staff to cover patients' injection sites. The requirement to cover injection sites to maintain blinding of the blinded rater is an acknowledgement that treating clinicians and patients who can see the injection sites are potentially unblinded. In addition, a potentially unblinded clinical investigator decides whether the findings of the blinded examiner "correlate" with the patient's symptoms after the examination is completed.

The frequency of disclosing side effects may be lower for daclizumab than for Avonex. Therefore, the blinding may have been more effective in Trial 201 with a placebo control than in Trial 301 with the active Avonex control.

The 12-week progression-of-disability events are also subjective. The protocol defines these events as a change in the (b) (4) EDSS scale.[40] This scale is essentially a complete neurological examination with over 100 items. An algorithm converts the neurological deficits to disability ratings ranging from 0-10. The neurological exam is

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[39] Expanded Disability Status Scale, MS Functional Composite, Visual Function Test.

[40] (b) (4). Expanded Disability Status Scale (EDSS) training and certification (b) (4) Cllinical Study Report for Trial 301.

itself subjective, highly dependent on the effort and attention of the subject and the judgment of the examiner. The protocol requires clinic visits to perform the EDSS every three months and acutely after the onset of a relapse. Dr. Rodichok points out in his review that the protocols do not clearly state whether or not the blinded examiner, treating physician, or patient can know the previous EDSS score at the time of the EDSS test.

An Independent Neurology Evaluation Committee (INEC) adjudicated relapse events that, in the opinion of the treating physician, met protocol criteria for a confirmed relapse. However, potentially unblinded investigators decided whether blinded evaluators would examine patients reporting relapse events and whether the relapse met protocol criteria. Potentially unblinded clinical investigators also determined whether the event was a relapse after reviewing the examination by the blinded examiner. The clinical investigators decided which events the INEC committee saw. The INEC did not adjudicate potential relapse events reported by patients but dismissed by the treating neurologist.

Blinding the rater does not control bias in the decisions and efforts made by patients and treating physicians. As Dr. Rodichok points out in his review, the patients and treating physicians contribute significantly to the determination that a relapse had occurred. Both are likely to be aware of unblinding side effects and both can introduce bias.

There is evidence that suggests blinding was not fully effective in Trial 301.

The sponsor argues that that bias did not meaningfully affect the study results because the relapse rates were similar in patients who did and did not report flu-like symptoms.[41] This review emphasizes that a further interpretation of this information is that bias was present and the effect size was smaller in the patients who reported relapses in both treatment arms. Table 10 summarizes the data the sponsor uses to support this conclusion. In Trial 301, 47% of Avonex-treated patients reported flu-like symptoms and may have guessed the identity of the study drug.[42] The relapse rates are "similar" for Avonex patients with and without flu-like symptoms (0.391 and 0.330) and for daclizumab patients (.292 and .203). Nevertheless, *patients with flu-like symptoms in both treatment arms reported* ***more*** *INEC-confirmed relapses and they had a smaller relative*

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[41] Module M2 ClinicalOverview.pdf, page 24 of 154.

[42] Some sources report higher rates for flu-like symptoms in Avonex-treated patients. For example, Ryan reports 61% in Table 2 in "Drug Therapies for the Treatment of Multiple Sclerosis," *Journal of Infusion Nursing*, Volume 32, May-June, 2009, pp. 137-144.

reduction in ARR, i.e., the apparent effectiveness of daclizumab was less in patients who had symptoms and were likely to think they were taking Avonex. This reduced effectiveness occurred in patients who may have thought they were receiving Avonex but were actually taking daclizumab. This observation is consistent with the presence of bias; to wit, patients who suspected they were on Avonex rather than daclizumab may have had expectations that Avonex was less effective than daclizumab and they would experience more relapses. Certainly, this is not substantial evidence that bias was present and this bias may not explain all of the effect of the daclizumab on relapse rate; however, the protocol does provide an opportunity for patients and treating physicians to make decisions biased by knowledge of informative adverse effect. Given this opportunity and the data in Table 10, it is reasonable to have concerns that bias introduced by the characteristic symptoms of Avonex explains an unknown portion of the observed effect on relapse rate and disability attributed to daclizumab in Trial 301.

Table 10 Relapse Rates by Presence of Flu-like Symptoms in Trial 301

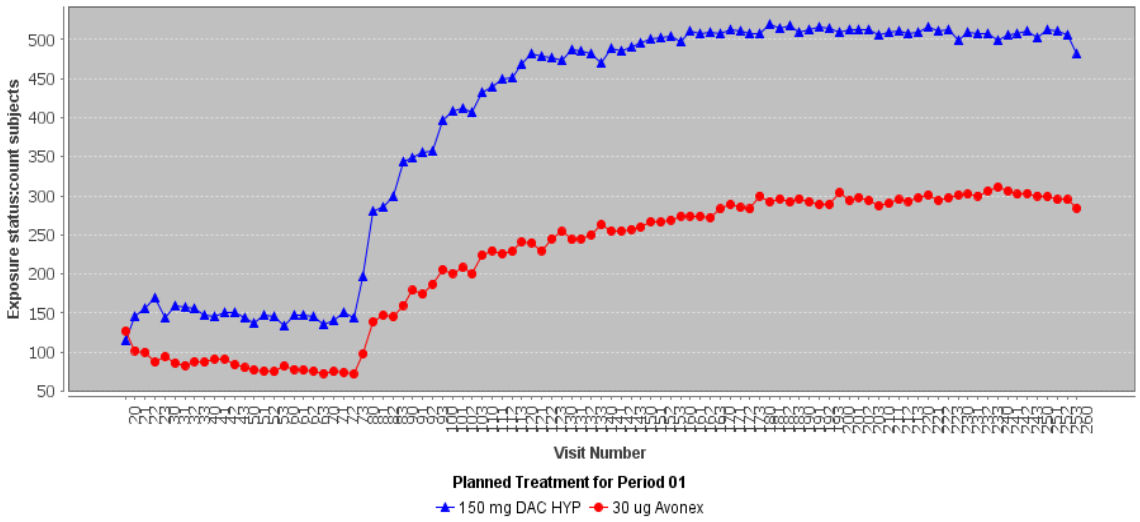
Relapse Rates by Presence of Flu-like Symptoms in Trial 301[43]				
	Avonex	Daclizumab	Total	Rate reduction
Flu-like symptoms				
Number of Patients	346	88	434	
Patients with Relapse	161 (47%)	28 (32%)	189 (44%)	
ARR	0.391	0.292		25.3%
Adjusted ARR	.434	.275		36.6%
Subject Relapse Rate	0.52	0.33		
No Flu-like Symptoms				
Number of Patients	576	831	1407	
Patients with Relapse	231 (40%)	232 (28%)	463 (33%)	
ARR	.330	.203		38.5%
Adjusted ARR	.363	.208		42.7%
Subject Relapse Rate	0.49	0.32		

In addition to this evidence of possible bias in relapse reporting, there is evidence of *bias in the concomitant treatment given patients after randomization* in the Avonex and daclizumab groups. Dr. Rodichok noted that patients and treating physicians behaved differently in the two study arms of Trial 301 when given the option at 24 weeks after starting treatment to stop taking NSAIDS prior to injecting Avonex. Approximately 200 more patients taking daclizumab chose to stop using NSAIDS than patients taking

[43] Trial 301 Clinical Study Report Table 89 (page 542 of 3937) and Table 90 (page 545 of 3937).

Avonex. This suggests that patients in both arms of the trial may have guessed their treatment assignment (Figure 5[44]). If so, some of the observed effect in the trial may have been due to bias.[45]

Figure 5 Trial 301 Subjects Who Did Not Use NSAIDs after Randomization.



Filter = EXCAT=NSAID; VisitNum<=260; EXSTAT=NOT DONE; Planned time = pre-injection

Data Quality and Protocol Compliance

Dr. Rodichok identified several indications of problems with data quality and trial conduct in Trial 301. These problems included submission of the statistical analysis plan and modifications to the hierarchy of secondary outcomes after randomization began and a high proportion of randomized subjects who did not complete the trial: 30%. For comparison, the proportion of patients who experienced no relapses differed in the Avonex and daclizumab groups by 15%. With a 30% dropout rate twice the effect size, the missing data could have significantly altered the Trial 301 outcome.

Another source of uncertainty is that the sponsor failed to collect the **protocol-required** *Suspected Relapse Questionnaire* for all patient-reported relapse events. The applicant did not collect this questionnaire when a potentially unblinded treating physician decided to disregard an event as a possible relapse. As a result, there is no record of some patient-reported relapse events. Blinded examiners did not examine patients who

[44] Copied from Dr. Rodichok's review

[45] Figure 5 also suggests that approximate 50 patients made informed decisions to stop NSAIDS before the end of the 24-week period that the protocol required all patients to take NSAIDS.

reported these events and the INEC did not have the opportunity to assess the treating physician's decision to disregard them.

The Trial 301 investigators did not evaluate relapses as quickly as the protocol required. The mean interval from the onset of symptoms to evaluation by the treating neurologist was 5.39 ± 5.96 days for the daclizumab group and 6.04±8.47 days for the Avonex group. The maximum time allowed by the protocol is 3 days. The protocol requires that the treating physician evaluate patients reporting suspected relapses within 48 hours of onset. The reported interval reported was 0 days for 70% of patients evaluated for suspected relapses in Trial 301. Dr. Rodichok finds it implausible that investigators evaluated this proportion of patients on the same day as symptom onset. He expresses doubts about the credibility of the dates and times recorded to document the relapse event confirmation process.

Trial Design Issues

For Trial 201, issues related to clinical trial design, conduct, and analysis are more serious than for Trial 301. Enrollment in Trial 201 began with a protocol that had MRI lesion count as the primary outcome, typical of early phase 2 exploratory proof-of-concept trials intended as preludes to adequate and well-controlled trials to provide evidence of safety and effectiveness in support of approval. However, 9 months after randomizing the first patient and enrolling approximately 155 subjects, the sponsor made major revisions to the protocol that included:[46]

1. changing the primary endpoint from *MRI lesions* to *relapse rate* at Week 52;
2. doubling the sample size from 297 to 594;
3. establishing a closed hierarchical sequential analysis for secondary outcomes[47]
4. changing the method of analysis of the ARR
5. adding exploratory endpoints to assess the effect on progression of disability
6. changing the method of determining the proportion of subjects who relapse
7. adding a futility analysis despite concern by FDA biostatistician[48]

These unplanned midstream changes may be acceptable for an exploratory trial to help choose a dose or determine a potential drug effect. They are generally not acceptable

[46] Amendment 5, protocol version 6, dated November 20, 2008. First randomization February 15, 2008, and the last visit August 30, 2011.

[47] The sequential analysis does not include any outcomes to assess disability progression

[48] July 14, 2009 COR-INDAD-02(Advice/Information Request)

for an adequate and well-controlled trial intended to provide substantial evidence to support a claim of safety and effectiveness.[49]

Another Trial 201 design issue is that after 24 weeks, the protocol allows subjects experiencing a relapse to start injecting IFN-β in addition to the study drug. Few patients took this option. Seven subjects began taking IFN-β, 5 in the placebo group and 1 each in the daclizumab 150 mg and daclizumab 300 mg groups.

There is a question whether the Trial 201 disability outcomes meet evidentiary criteria because they were never pre-specified primary or secondary outcomes.

Trial 201 was one-year in duration. Most "pivotal" MS trials observe patients for two years. The most uncertainty about the 12-week sustained disability outcome occurs in the 12-weeks before the subject completes the trial and the first 12-weeks at the beginning of the trial when subjects may still be adjusting to a new treatment. With a 52-week trial, a much higher proportion of sustained disability progression events will occur during these periods of higher uncertainty. With 12 weeks between visits, there are only three EDSS measurements after baseline before the trial ends.

The sponsor makes plausible post-hoc arguments that the observed small reductions in disability progression associated with daclizumab in Trials 301 and 201 are statistically significant. For trial 301, plausibility that daclizumab reduces disability progression more than Avonex requires assumptions that bias did not significantly affect dropout or EDSS scores even though there is evidence that bias was present. It also requires the post hoc assumption that Trial 301 is a valid noninferiority trial for disability despite weaknesses in overall performance and data quality.

Efficacy Conclusion

This review concludes that there is evidence that Daclizumab reduces the annualized relapse rate in patients with relapsing multiple sclerosis compared to Avonex and placebo. However, the BLA does not contain substantial evidence that daclizumab reduces the number of episodes of 12-week disability progression.

[49] FDA Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics. 2010. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064981.htm

8. Safety

Lourdes Villalba, MD, the primary safety reviewer, has serious concerns about the safety of daclizumab. She recommends against approval unless efficacy is overwhelming. If the benefits of daclizumab outweigh the risks, the secondary safety reviewer, Sally Jo Yasuda, Pharm.D., recommends approval with a requirement for a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) and prescribing information that includes a boxed warning, recommendations for stringent patient monitoring, and a Medication Guide for the patient.

In brief, the safety reviews identify major and potentially life-threatening safety events associated with daclizumab that include drug-induced liver injury (DILI), serious immune-mediated reactions, infections, seizures, malignancies, depression, and suicidality. There is no way to predict which patients will experience any of these serious events before starting treatment. The events occurred throughout the course of therapy; some after discontinuation of daclizumab. Some of these events resolved months after discontinuing daclizumab and some required invasive procedures for diagnosis or treatment with additional immunosuppressive medications.

Quality of Safety Data

FDA extended the review period by three months because the sponsor submitted extensive amendments to provide adequate safety data not in the original application. Even with the additional safety data, Dr. Villalba found inadequate follow-up of adverse events and events categorized as non-serious when in fact they were serious. Dr. Villalba found descriptions of serious events in patient narratives that she could not find in the AE dataset; drug withdrawals appeared as interruptions. She is concerned that the incomplete reporting may lead to an underestimate of the toxicity of daclizumab.

Exposure

Three clinical trials and associated extension studies in RRMS patients are the source of the safety data: trials 201, 301, and 302 (see Table 12 and Figure 6).

At the time of the Safety Update (SUR), 2236 patients (~5200 patient-years) had taken daclizumab; 1785 of these were patients with MS (~4100-patient years). For MS patients, the mean number of 150mg doses was 26; the maximum was 74.[50] See Table 11.

[50] iss-scs-tables-figures.pdf, daclizumab/0000/m2/27-clin-sum, Table 16, page 42 of 6938.

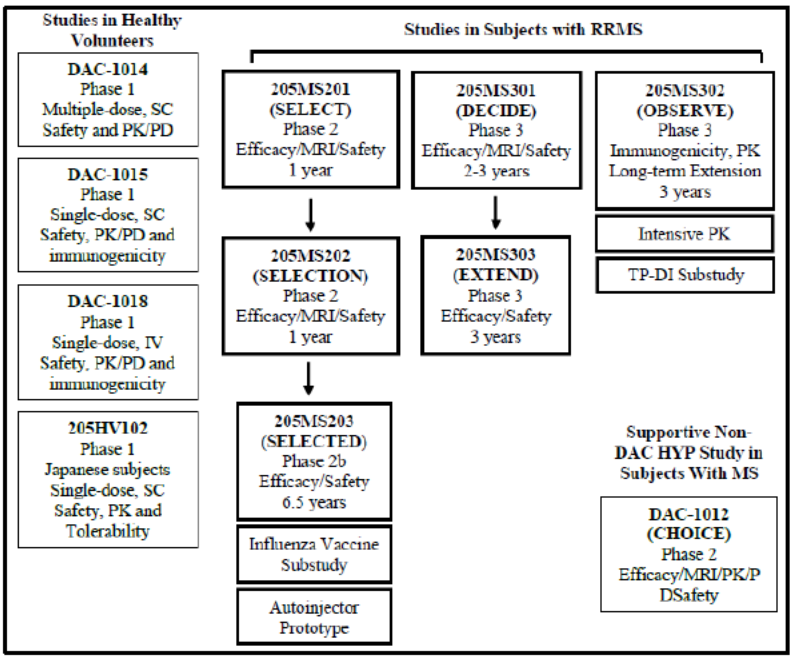
Table 11 Number of Months of Exposure to Daclizumab

Number of patients with RMS exposed to daclizumab 150 mg or higher:			
Any exposure	12 months	24 months	36 months
2236	1576	1259	888

Table 12 Trials that provided safety data for daclizumab[51]

Trial Identity	Trial Design	Dosage	Primary Study Endpoint	Treatment Duration	Subjects
Study 201	RCT	150 mg or 300 mg q4W	ARR	52 weeks	621
Study 301	RCT	150mg q4W	ARR	96 weeks	1841
205MS 202	Extension	150 mg or 300 mg q4W	Safety	52 weeks	517
205MS 203	Extension	150 mg q4W	Safety	Up to 6.5 years	410
205MS302	Extension	150 mg q4W	PK		133
205MS303	Extension	150 mg q4W	Safety	Up to 144 weeks	1033

Figure 6 Clinical Studies in the Development of Daclizumab



[51] From Table 3 in Dr. Rodichok's Efficacy Review.

Overview of Adverse Events

SAEs and discontinuations due to the study drug occurred more often in groups treated with daclizumab than placebo in Trial 201 or Avonex in Trial 301. A similar number of total adverse events occurred in all treatment groups in both trials. See table below extracted from Dr. Yasuda's review (Table 13).

Table 13 SAE's, Discontinuations, and Treatment Emergent Adverse Events (TEAEs) in Trials of Daclizumab

Percent of Patients with SAEs, Discontinuations, or TEAEs (excluding MS relapses)						
	Study 201 1 Year Study			Study 301 2-Year Study		Total DAC in all trials
	Placebo	DAC 150	DAC 300	Interferon beta-1a	DAC	
Subjects	204	207	208	922	919	2236
All Serious AEs[52]	5.9%	7.2%	8.7%	9.4%	15.5%	15.7%
Discontinuations	1%	2.9%	3.8%	9.0%	14.3%	12.9%
TEAEs	69%	72%	73%	91%	88%	82%

The remainder of this section summarizes the safety information under Deaths, Severe Adverse Events, Safety Events of Concern, and Common Adverse Events. Analyses of adverse events include events with onset up to 180 days after study drug discontinuation because of the long half-life of DAC.

Deaths

Dr. Villalba concluded that 2 of 5 deaths in daclizumab treated patients are related to the drug; one was due to autoimmune hepatitis and the other to an infection resulting from a skin reaction. There were 5 deaths in the Avonex control group, none related to Avonex. See Table 14, below, for details.

After patient 909-001 in Trial 201 died, the sponsor amended active protocols to require monthly liver function tests prior to all injections and interruption of study drug if ALT values exceeded 3 times the upper limit of normal (ULN), bilirubin exceeded 2 times the ULN, or there was any other clinically significant hepatic test abnormality in the opinion of the Investigator. Drs. Yasuda and Villalba recommend continuing the monthly laboratory testing if daclizumab is approved.

[52] Excluding serious relapses.

Table 14 Deaths in Clinical Trials[53]

Trial ID	Age Sex	Last dose/ Death (Study day)	Cause of death	Drug Related
Daclizumab 150 mg				
201 304-006	49 F	308/402	Serious cutaneous drug reaction, complicated with psoas abscess and ischemic colitis. Transaminase elevation on Day 169 leading to drug discontinuation on Day 308. Maculopapular rash on Day 326, followed by bilateral retinal vein thrombosis, ischemic colitis, and psoas abscess.	**Yes**
301 431-004	37 F	58/179	MS progression. Aspiration pneumonia. Septic shock. MS relapse and small bowel obstruction later complicated with aspiration pneumonia. Had discontinued drug because of eczema	
301 744-007	46 F	85/202	MS relapse and aspiration pneumonia on Day 95. Developed quadriplegia and swallowing problems, treated with azathioprine. Sepsis and cardiorespiratory arrest were reported on Day 202.	
303 537-012	39 F	171/193	Traumatic subdural and subarachnoid hemorrhage. Patient had received DAC 150 during study 301. She fell in the bathroom on Day 184 of study 303 and died of cerebral hemorrhage.	
Daclizumab 300 mg				
202 909-001	45 F	225/325	Autoimmune hepatitis, liver failure, multiorgan failure. Patient received DAC 300 in study 201, 5 doses of placebo in 202 (6 months off-daclizumab); re-started DAC 300 (4 doses) with rapid ALT increase and decline in liver function leading to death.	**Yes**
IFN β-1a				
301 536-005	40 M	115/145	Acute myocardial infarction. Hx of HTN, coronary artery disease, prior MI & coronary stenting nine months prior to study entry. No additional information is available.	
301 558-001	43 F	142/148	Peritonitis after laparotomy for abdominal pain after 20 weekly doses of IFN. No additional information is available.	
301 641-026	41 M	414/446	Suicide. No psychiatric history or known risk factors. It occurred 32 days after last dose of INF. He had received 60 doses. No additional information is available.	
301 658-010	53 M	863/924	Pancreatic cancer 2 months after last dose. Hospitalized for neuropathic pain. CT scan showed pancreatic ca with metastatic disease of lung and liver.	
301 741-002	28 M	55/284	Progression of MS approximately 7 months after stopping IFN.	

[53] Adapted from Table 10 on page 50 of 395 in Dr. Villalba's primary safety review.

Serious adverse events

Dr. Villalba identified a number of important serious safety concerns that occurred more often in subjects receiving daclizumab than either placebo (Trial 201) or Avonex (Trial 301). Serious adverse events continued to occur over several years of therapy. Some safety events identified as SAEs in the controlled trials also resulted in daclizumab discontinuation.

In Trial 301 and 201, relapses can be adverse events. Any serious adverse event is likely to be disabling to some extent.[54] There were 3.0% more of daclizumab subjects with serious adverse events than Avonex patients including serious relapses. Excluding relapse SAEs, the difference doubles to 5.9%. See Table 15. In Trial 201 the serious adverse event rate is higher in the placebo group because of serious relapses. SAEs excluding serious relapses are similar in all 3 treatment groups. See

Table 16.

Table 15 Trial 301 Rates of SAEs With and Without Serious Relapses

Trial 301 Number of Subjects with Serious Treatment Emergent Adverse Events[55]			
	Avonex	Daclizumab	Difference
Number of Subjects`	922	919	
Any SAE	194 (21.04%)	221 (24.05%)	3.01%
SAEs Except Relapse	88 (9.54%)	142 (15.45%)	5.91%

[54] 21 CFR 312.32(a): An adverse event … is considered "serious" if it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[55] Trial 301 Clinical Study Report. Table 43. Page 241 of 3937.

Table 16 Trial 201 Rates of SAEs With and Without Serious Relapses

Trial 201 Number of Subjects with Serious Treatment Emergent Adverse Events[56]			
	Placebo	Daclizumab 150	Daclizumab 300
Subjects`	204	208	209
Any Treatment Emergent SAE	52 (25%)	29 (14%)	34 (16%)
Treatment Emergent SAEs Except Relapse	12 (6%)	15 (7%)	19 (9%)

Safety issues of concern

The safety reviews identified the following adverse events as issues of concern:

- Drug-induced liver injury (DILI) that includes 1 death, 1 liver failure, and many cases of DILI
- Immune/Autoimmune-Mediated Reactions (not including skin reactions), including colitis, sarcoidosis, celiac disease, interstitial lung disease, vitiligo, hemolytic anemia, thrombocytopenia, diabetes mellitus, glomerulonephritis (n=2), rheumatoid arthritis that required invasive procedures to diagnose and prolonged immunosuppressive therapy with steroids or azathioprine to treat; inflammatory syndromes with multi-organ failure; and lymphadenopathy.
- Skin Reactions
- Acute Hypersensitivity, including anaphylaxis and angioedema
- Possible Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and other Systemic Inflammatory Reactions
- Infections
- Depression and Suicide
- Seizures
- Malignancies, in particular breast cancer and non-Hodgkin lymphoma
- Lymphadenopathy

This review describes each of these issues of concern under italicized headings below.

[56] Trial 201 Clinical Study Report. Table 154. Page 845 of 1641.

--Drug-induced liver injury (DILI)

Dr. Yasuda agrees with Dr. Villalba that daclizumab is associated with DILI. They are both concerned about patient safety because the onset of DILI is unpredictable, occurs despite monitoring, can be fatal, and there is no way to identify susceptible patients.

There was one death due to DILI. The patient took thirteen 300 mg doses in Trial 201 and then four doses of placebo in Trial 202. ALT was 1.3 x ULN at screening but normal from baseline through week 32 in Trial 201. After week 32, ALT was increased but not more than 2 x ULN until she completed Trial 201 and entered study 202. In Trial 202, she took placebo for 6 months. She had a relapse treated with methylprednisolone and tizanidine, a hepatotoxic muscle relaxer, one month before she restarted daclizumab 300 mg. After restarting, there was a progressive rapid ALT increase and decline in liver function. She died of liver failure after taking four 300 mg doses one month apart.

After this death, the applicant modified the Trial 301 protocol. The change required the treating neurologist to temporarily stop treatment with the study drug until results of liver function tests (ALT, AST, and total bilirubin) performed no more than 7 days prior to administration were available. Investigators were to required to temporarily suspend treatment if ALT or AST was more that 3 x ULN or total bilirubin was more than 2 x ULN. Study treatment could restart if, within 8 weeks of stopping treatment, ALT and AST levels fell to 2 x ULN or below and total bilirubin to 1 x ULN or below. If levels remained above these values for 8 weeks, then the protocol required permanent discontinuation. The protocol also required permanent discontinuation if, after restarting treatment, levels exceeded criteria for suspending treatment a second time.

Drs. Villalba and Yasuda emphasize the following in their review of adverse events related to DILI:

- Transaminase elevations for daclizumab were greater than for control in the controlled trials. Elevations of ALT or AST occurred in more than 5% of daclizumab-treated patients and more often in daclizumab-treated patients than Avonex-treated or placebo-treated controls.
- At least 4 Hy's law cases were identified in the clinical trial database for which a role for DAC cannot be ruled out.[57]

[57] In her review, Dr. Yasuda writes that "finding 2 Hy's law cases in a clinical trial database is considered highly predictive that the drug has the potential to cause severe DILI (fatal or requiring transplant) when given to a larger population, at a rate of about 1/10th the rate of Hy's law cases. The role of DAC cannot be ruled out in at least 4 Hy's law cases; that is a rate of at least 4/2336 (about 9/5,000); the potential to

- At least 7 cases of DILI (2 of the Hy's law cases, including the death) were autoimmune hepatitis (AIH). Some of these AIH cases did not have the characteristic serum autoantibodies (such as ANA) of idiopathic AIH.
- In all studies, there were 21 DILI SAEs. Eight of these patients received high dose corticosteroids, including 3 also treated with azathioprine, for suspected autoimmune hepatitis (AIH)

Dr. Yasuda and Dr. Villalba requested reviews of hepatic events from Drs. Mark Avigan and John Senior in the FDA Office of Pharmacovigilance and Epidemiology. Dr. Avigan stated *"it is unlikely that any risk mitigation strategy including periodic serum biochemical monitoring would fully eliminate risk for a life-threatening clinical adverse outcome.*" His reasons are the broad inter-and intra-individual variability of the clinical presentation, the time to onset and severity of episodes of idiosyncratic DILI, including drug-induced AIH, and the rapid acceleration of organ injury that may occur in some cases." Dr. Senior, in general, agrees with this statement and the reasons. However, Dr. Avigan concludes, "nonetheless, regular assessments and monitoring at regularly scheduled appointments … are likely to reduce serious outcomes." Dr. Senior disagrees with this conclusion because data in the current submission do not demonstrate that intensive monitoring prevents serious adverse events and because he doubts there will be compliance with monitoring requirements.

Dr. Senior places the assessment of risk in the context of other available treatments and the likelihood and extent of beneficial effects. "I am not impressed that daclizumab fills an unmet need, as claimed by Biogen, but am quite alarmed at the high frequency of serious liver toxicity, especially that appearing like a form of autoimmune hepatitis that progresses despite stopping its administration. … This is a new and ominous kind of DILI, where the usual adaptation is not enough to overcome the delayed immunological attack on hepatocytes triggered by the daclizumab." He also states that if the drug is approved, the sponsor should track all patients treated to determine "whether they get the benefits claimed on not, and to determine the actual incidence of unintended effects."

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cause severe DILI would be predicted to be about at least 2/10,000 (if the cases of AIH have the same implications as the non-AIH cases)."

Table 17 Percent of Patients with Liver-Related Events and Elevated ALT

Percent of Patients with Liver-Related Events and Elevated ALT[58]					
	Study 201			Study 301	
	DAC 150	DAC 300	Placebo	DAC 150	Avonex
Patients in treatment group	N=207	N=208	N=204	N=919	N=922
SAE Hepatobiliary[59]	1.4%	0.5%	0.5%	0.9%	0.8%
SAE of DILI	1.0%	0.5%	0.0%	0.5%	0.1%
Hepatobiliary dropouts	1.4%	0.5%	0.5%	5.3%	3.9%
ALT more than 5 x ULN	4.3%	3.8%	1.0%	5.8%	3.2%
ALT more than 10 x ULN	3.4%	1.4%	0.0%	2.6%	1.2%
ALT more than 20 x ULN	1.4%	1.0%	0.0%	1.0%	0.4%
ALT greater than 3xULN, BR greater than 2xULN, ALP[60] less than 2xULN	0.5%	0.5%	0.5%	0.7%	0.1%

Dr. Yasuda's review notes that DILI has no known risk factors and occurs despite monitoring. Consequences include death and liver failure. She recommends a Boxed Warning for DILI and stringent monitoring. As noted by Drs. Villalba and Avigan, monitoring may not fully eliminate the risk of a life-threatening hepatotoxic event.

--Immunity-Mediated and Autoimmunity-Mediated Adverse Reactions

Dr. Villalba compiled a list of potential immune-mediated events. Using a customized MedDRA Query, she identified 619 (27.7%) patients with potential immune-mediated reactions in the daclizumab database. This review summarizes her list in Table 18, below. Only events that occurred in 4 or more patients are listed in the table.

[58] Adapted from Dr. Yasuda's review in section on DILI under Specific Safety Issues
[59] *Hepatobiliary refers to the Hepatobiliary disorders SOC and Investigations SOC, Hepatobiliary HLGT. These SOCs include AE of cholecystitis and biliary colic that are not drug induced liver injury.
[60] Serum alkaline phosphatase

Table 18 Potential Immune-Mediated Events

Subjects with Immune Mediated Events in Entire Daclizumab Safety Database[61]		
Patients in Database	2236	100%
All Immune-mediated Events	619	27.7%
Dermatitis/Eczema	305	13.6%
Lymphadenopathy	137	6%
Psoriasis	48	2%
Enteropathy	28	1.2%
Immune Mediated Hepatitis	11	0.5%
Sarcoidosis	9	0.3%
Cutaneous or Systemic Vasculitis	7	0.3%
Celiac Disease	4	0.2%
Immune Thrombocytopenia	4	0.2%

The sponsor submitted an analysis of allergic and autoimmune events in Trial 201, Trial 301, and the entire DAC-treated population. The results, summarized in Table 19, below, confirm that there were more events in the daclizumab group than either the Avonex or the placebo groups in the two confirmatory trials.[62] In trial 301, 3% of subjects had serious non-cutaneous severe adverse events.

Table 19 Allergic and Autoimmune Events Excluding Cutaneous Events

Subjects with Allergic And Autoimmune Mediated Events Excluding Cutaneous Events[63]				
Group	N	Drug	All AEs	Serious AEs
Trial 201	209	DAC 150	7%	0%
	208	DAC 300	8%	less than 1%
	204	Placebo	3%	0%
Trial 301	919	DAC 150	18%	3%
	922	Avonex	6%	less than 1%
Total DAC pool	2236	DAC	17%	3%

[61] Table adapted from summary in Dr. Yasuda's review. The sponsor reported 18% for all immune-related events with daclizumab and 6% for Avonex.

[62] In her review, Dr. Villalba notes that the Avonex label warns of increased autoimmune disorders: "Postmarketing reports of autoimmune disorders of multiple target organs in AVONEX-treated patients included idiopathic thrombocytopenia, hyper-and hypothyroidism, and rare cases of autoimmune hepatitis. If AVONEX-treated patients develop a new autoimmune disorder, consider stopping the therapy."

[63] Derived from Table 1 in response-to-ir-received-18feb16-q4.pdf submitted by sponsor or March 7, 2016.

The sponsor excluded eczema and other rashes from their analysis of immune-mediated events summarized above in Table 19. They identified 373 patients who experienced at least one potential immune-mediated event in the total daclizumab database. Dr. Villalba writes that "of the 373, 40 (10.7%) were treated with systemic oral, intravenous or intramuscular corticosteroids; 6 (1.6%) were treated with azathioprine, and 3 (0.8%) with methotrexate. Of the 373, 174 had immune-mediated reactions that had not resolved as of March 3, 2016 (174/373 = 47% of all immune-mediated reactions)." The immune-related disorders included colitis, sarcoidosis, celiac disease, interstitial lung disease, vitiligo, hemolytic anemia, thrombocytopenia, diabetes mellitus, glomerulonephritis, and rheumatoid arthritis.

--Skin Reactions

Skin reactions occurred in 40% of daclizumab-treated patients. Some were serious. Fewer skin reactions occurred in patients treated with placebo or Avonex in Trials 201 and 301. Table 20 , below shows that skin reactions occurred more often in daclizumab than placebo and Avonex-treated patients. The number of serious skin reactions with daclizumab is notable when compared to the low proportion of subjects in the Avonex and placebo groups. Serious events included rash, exfoliative dermatitis, allergic dermatitis, atopic dermatitis, erythema nodosum, dermal cyst, angioedema (2), leukocytoclastic vasculitis, potential DRESS, psoriasis (2), and toxic skin eruption. Clearly, many of these serious reactions are potentially immunologic.

Table 20 Skin and Subcutaneous Tissue Disorders

Skin and Subcutaneous Tissue Disorders Percent of Subjects[64]						
	Study 201			Study 301		Total DAC
	Placebo	DAC 150	DAC 300	Avonex	DAC 150	DAC
SAEs	0%	1%	1.4%	0.1%	1.5%	2%
Discontinuations	0%	1.4%	1.4%	0.8%	4.7%	4%
TEAEs	12.7%	15.9%	18.3%	19.1%	37.3%	40%
Rash[a]	1%	7%	7%	4%[c]	10%[c]	9%
Dermatitis- and Eczema-Related Terms	2%	3%	6%	6%[c]	14%[c]	14%

[64] Adapted from Dr. Yasuda's review.

--Acute Hypersensitivity, including anaphylaxis and angioedema

Events of acute hypersensitivity included angioedema, anaphylaxis, and serious urticaria. Acute hypersensitivity events occurred throughout the DAC treatment period and lasted for as long as 201 days.

Dr. Villalba identified 80 cases of angioedema in subjects treated with daclizumab. In Study 301 Dr. Villalba identified 23 (2.5%) patients on DAC vs 11 (1.2%) on Avonex with AEs consistent with angioedema. Six subjects had angioedema events categorized as serious, severe, or leading to drug withdrawal.

--Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and other Systemic Inflammatory Reactions

DRESS is a severe systemic disease with fever, rash, lymphadenopathy, and visceral organ involvement. There is hepatitis in 50-60% of cases, eosinophilia in 70-90% of cases. DRESS can have a long-lasting clinical course after withdrawal of the causative drug. Dr. Villalba identified 3 patients with findings suggestive of DRESS and that are included among the immune- and autoimmune-mediated adverse events discussed above.

--Infections

There were more infections in daclizumab-treated groups than the comparator groups in Trials 201 and 301. 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.

Table 21 Infections

Infections[65] Percent of Subjects						
	Study 201			**Study 301**		**Total DAC**
	Placebo	DAC 150	DAC 300	Avonex	DAC 150	DAC
SAEs	0%	2.9%	1.5%	1.6%	4.6%	4.4%
Discontinuations	0%	0.5%	0.5%	0.3%	0.5%	0.8%
TEAEs	44%	50%	54%	57%	65%	59%

[65] Adapted from a table in Dr. Yasuda's review.

--Depression and Suicide

In her review, Dr. Yasuda notes that AEs related to suicide occurred in 0.5% of subjects on Avonex and 0.5% of those on DAC. Depression occurred in 2% of subjects taking placebo and 7% of subjects on DAC 150 and 300 in Trial 201. In Trial 301, 10 % of subjects on daclizumab 150 reported depression compared to 7% taking Avonex. The safety review team recommends inclusion of a warning about the potential for depression similar to that in the Avonex label.

--Seizures

More seizures occurred in the daclizumab subjects than in Avonex subjects in Trial 301 (1.2% vs. 0.3%). The safety team recommends a warning for seizures similar to that in the Avonex label. See also *HepatotoxicDrugs* above on page 14.

--Malignancies, in particular breast cancer and non-Hodgkin lymphoma

Melanoma occurred in 2 patients taking daclizumab in Trial 201. Otherwise malignancies were balanced across treatment groups in Trials 201 and 301. Breast cancer occurred in 8 females and 1 male in the extension studies at rates greater than that in the background population. There were 3 cases of non-Hodgkin's lymphoma (NHL) in extension studies. Given that there was a case of breast cancer in a male, a possibly increased rate of breast cancer in females, and a rate of NHL greater than background, Dr. Yasuda recommends including these malignancies in the labeling and assessing cancer risk in a post-marketing study.

--Lymphadenopathy

There are more TEAEs related to lymphadenopathy in the daclizumab group than in the Avonex group in the Study 301 (6% vs 1%). See Table 22. Seven subjects had a biopsy or fine needle aspiration. The pathology was benign reactive hyperplasia in all seven cases. Dr. Yasuda recommends that the label mention lymphadenopathy because lymphadenopathy can indicate the presence of disease that requires treatment.

Table 22 Lymphadenitis, Lymphadenopathy, or Lymphoid Tissue Hyperplasia

Lymphadenitis, Lymphadenopathy, or Lymphoid Tissue Hyperplasia SAEs, Discontinuations, and TEAEs Percent of Subjects						
	Study 201			Study 301		Total DAC
	Placebo	DAC 150	DAC 300	Avonex	DAC 150	DAC
SAEs	0%	0%	0.5%	0%	1.0%	1.6%[a]
Discontinuations	0%	0%	0%	0%	0.5%	0.6%[b]
TEAEs	1%	2%	1%	1%	6%	6.1%[b]

Common Adverse Events in the 201 and 301 Trials

For the drug label, the safety review team has summarized the incidence of more common adverse events in two tables that include the events in the control arm for comparison. See Table 23 and Table 24, below:

Table 23 AEs More Frequent with Daclizumab than Placebo in Trial 201

Adverse Events in More Than 5% of Subjects in Trial 201 More Frequent with Daclizumab than Placebo Percent of Patients				
Body System or Organ Class	**Adverse Event**	**Placebo**	**Daclizumab 150**	**Daclizumab 300**
Infections	Respiratory Tract Infection	8%	7%	11%
	Upper Respiratory Tract Infection	7	9	10
	Pharyngitis	4	6	6
	Oral Herpes	5	5	6
	Influenza	5	2	6
	Urinary Tract Infection	4	4	5
General Disorders	Pyrexia	1	3	7
Psychiatric Disorders	Depression, Depressed Mood	2	7	7
Investigations	ALT increased	2	5	6
Skin and Subcutaneous Tissue Disorders	Rash	1	7	7
	Dermatitis- and Eczema-Related	2	3	6

Table 24 AEs More Frequent with Daclizumab than Avonex in Trial 301

Adverse Events in More Than 5% of Subjects in Trial 301 More Frequent with Daclizumab than Avonex Percent of Patients			
Body System or Organ Class	**Adverse Event**	**Avonex**	**Daclizumab**
Infections	Nasopharyngitis	21%	25%
	Upper Respiratory Tract Infection	13	16
	Influenza	6	9
	Pharyngitis	8	8
	Bronchitis	5	7
	Oral Herpes	5	6
Skin and Subcutaneous Tissue Disorders	Dermatitis- and Eczema-related	6	14
	Rashes, Eruptions, and Exanthems	4	10
Musculoskeletal and Connective Tissue Disorders	Back Pain	8	9
	Arthralgia	7	8
	Extremity Pain	6	6
	Myalgia	5	5
Psychiatric Disorders	Depression, Depressed Mood	7	10
General Disorders	Fatigue	8	8
Investigations	ALT Increased	7	8
	AST Increased	5	5
Respiratory, Thoracic, and Mediastinal Disorders	Oropharyngeal Pain	4	8
	Cough	5	6
Gastrointestinal Disorders	Diarrhea	6	7
	Nausea	5	5
Nervous System Disorders	Hypoaesthesia	6	6
	Dizziness	4	5
Blood and Lymphatic System Disorders	Lymphadenopathy	0.8	5

9. Advisory Committee Meeting

There are no plans for an advisory committee meeting.

10. Pediatrics

Because of the significant safety concerns in adults discussed in section 8, above, this review recommends against the use of daclizumab in children. The Division of Pediatric and Maternal Health reviewed the DNP proposal and agree that the label should state that daclizumab is not for use in pediatric patients. The Pediatric Review

Committee agreed with the Division's plan for a full waiver and requested that the labeling reflect the safety concerns in section 8.4.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

Prescribing Information

The review team recommends that the daclizumab label contain a boxed warning about hepatic injury including autoimmune hepatitis and other immune disorders.

FDA labeling guidelines[66] and previous advice to the applicant would suggest that no disability outcomes would be included in the daclizumab label because the 12-week disability outcome failed to achieve statistical significance as defined in the statistical analysis plans for the two confirmatory trials. [67]

Labels for 10 of 11 different FDA-approved MS drugs report disability progression outcomes.[68] In some of these labels, the disability outcomes are not all statistically significant, but all labels except the Copaxone and Novantrone[69] labels contain at least one trial that showed a statistically significant effect (p-value less than 0.05) for a disability progression outcome at two years. All the statistically significant results applied to two years of observation and the comparator was placebo in all but the

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[66] Guidance for Industry. Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. 2006. Page 5. "Primary and Secondary Endpoints: The terms primary endpoint and secondary endpoint are used so variably that they are rarely helpful. The appropriate inquiry is whether there is *a well-documented, statistically and clinically meaningful effect on a prospectively defined endpoint*, not whether the endpoint was identified as primary or secondary.

[67] While DNP did agree to the primary ARR outcome after a Special Protocol Assessment, they warned the applicant that no consideration for inclusion in labeling would be given to exploratory endpoints or secondary endpoints that did not meet the pre-specified hierarchical plan for multiplicity adjustment in the statistical analysis plan. In response to the statistical analysis plan for Trial 201, the statistician informed the sponsor that "The secondary endpoints should adhere to the following criteria in order to possibly be considered for inclusion in labeling: 1) An endpoint capturing values that are also captured by the primary endpoint will normally not be eligible for inclusion in labeling. 2) Secondary endpoints need to have multiplicity adjustment at a family-wise type-I error of 0.05." Russell G. Katz. IND 12120 Advice/Information Request from FDA to Facet Biotech Corporation July 14, 2009.

[68] Appendix, Table 25

[69] The Novantrone label includes a statistically significant difference in EDSS at 6 months in one study.

alemtuzumab label where the positive trial was an open label trial with Rebif as the comparator.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

At a meeting on March 8, 2016, the REMS Oversight Committee (ROC) discussed the need for risk management efforts beyond the product labeling to ensure that benefits of daclizumab outweigh its risks. The Division anticipates low usage because the safety profile of the drug has been widely reported in the multiple sclerosis community. Prescribers are already aware of the risks and the proposed indication would be in a very narrow population of MS patients who had not responded to at least two other therapies. The proposed label is for a narrower indication than the studied population. The Division also anticipates that neurologists who are MS specialists would be the primary prescribers. If FDA approves daclizumab without a REMS that includes Efforts to Assure Safe Use (ETASU), the community could perceived that FDA believes daclizumab is safer than other drugs approved with similar risks, which is not necessarily the case. The ROC recommended a REMS with ETASU. The focus of the REMS will be to assure monthly laboratory testing prior to each dose of the drug.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

PMR's are currently under discussion.

14. Recommended Comments to the Applicant

None.

Appendix

Table 25 Disability Progression in Approved Drug Labels for MS Products

Sustained Disability Progression in Approved Drug Labels for MS Products										
Drug	**Name**	Number of Trials in Label	Trials with SAD outcomes	Trials with SAD p-value	Arms with SAD outcome	Arms with SAD p-value	SAD outcomes in label	SAD with p-value < 0.05	Two statistically significant SAD results in two arms	Two statistically significant SAD results in two separate trials
Novantrone	mitoxantrone	2	0	0	0	0	0	0	No	No
Betaseron[70]	interferon β-1b	4	2	1	2	1	2	1	No	No
Avonex	interferon β-1a	2[71]	1	1	1	1	1	1	No	No
Copaxone	glatiramer acetate	5	2	2	2	2	2	0	No	No
Rebif	interferon β-1a	2	1	1	2	2	2	2	Yes[72]	No
Tysabri	natalizumab	2	2	2	2	2	2	2	Yes	Yes
Gilenya	fingolimod	2	2	2	1	2	2	1	No	No
Aubagio	teriflunomide	4	2	2	4	4	4	2	Yes[73]	Yes
Tecfidera	dimethyl fumarate	2	2	2	2	2	2	1	No	No
Plegridy	interferon β-1a	1	1	1	1	1	1	1	No	No
Lemtrada	dimethyl fumarate	2[74]	2	2	2	2	2	1	No	No
Zimbryta[75]	daclizumab	2	2	2	3	3	3	0[76]	No	No

[70] Also marketed and labeled with same data as Extavia.
[71] The trial which compared Rebif to Avonex was open label.
[72] Two doses in same trial
[73] Two statistically significant results for higher of two doses in two separate trials.
[74] Both trials were open label
[75] No approved label. Table entries represent data available in NDA, not in label.
[76] Trial 201 had a nominally significant effect on disability progression in an exploratory outcome.

Table 26 Sustained Accumulation of Disability As Described in Labels of Approved MS Drugs for RMS

Sustained Accumulation of Disability As Described in Labels of Approved MS Drugs for RMS

Drug	Study Number	Type of MS	Size of Treatment Arm	Trial Duration in Years	Blinding	Primary Endpoint	Treatment Arm (placebo unless specified)	Sustained Accumulation of Disability Proportion of Patients								
								Duration of Progression in Months	Placebo	Active Comparator	Drug	p-value	Relative Risk Placebo	Realtive Risk Active Comparator	Absolute Difference	Number Needed to Treat
Novantrone	1	RMS	60	2	?	Composite	mitoxantrone 12mg 3 month									
Novantrone	2	RMS	21	0.5	OL	MRI	mitoxantrone added to steroids									
Betaseron	1	RRMS	124	2	DB	ARR	beta interferon 1b									
Betaseron	2	SPMS	360	3	DB	SAD	beta interferon 1b	?	0.19		0.16	0.005	0.84		0.03	33.3
Betaseron	3	SPMS	317	3	DB	SAD	beta interferon 1b	?	0.12		0.12		1		0	
Betaseron	4	CIS	292	2	DB	ARR	beta interferon 1b									
Avonex	1	RRMS	158	2	DB	SAD	beta interferon 1a	6	0.35		0.22	0.02	0.63		0.13	7.7
Avonex	2	RRMS	193	2	DB	ARR	beta interferon 1a									
Copaxone	1	RRMS	25	2	DB	Relapse Free	glatiramer acetate	3	0.48		0.2	0.07	0.42		0.28	3.6
Copaxone	2	RRMS	125	2	DB	ARR	glatiramer acetate	3	0.25		0.22	0.48	0.88		0.03	33.3
Copaxone	3	CIS	243	3	DB	Relapse Free	glatiramer acetate									
Copaxone	4	RRMS	119	0.75	DB	MRI Lesions	glatiramer acetate									
Copaxone	5	RRMS	943	1	DB	ARR	glatiramer acetate									
Rebif	1	RMS	184	2	DB	ARR	beta interferon 1a 44ug tiw	3	0.37		0.29	0.04	0.7824		0.08	12.5
Rebif	1	RMS	189	2	DB	ARR	beta interferon 1a 22ug tiw	3	0.37		0.26	0.01	0.702		0.11	9.1
Rebif	2	RMS	339	1	OL	Relapse Free	beta interferon 1a 44ug vs. Avonex									
Tysabri	1	RMS	627	2	DB	SAD	natalizumab 300mg	3	0.29		0.17	0.001	0.59		0.12	8.3
Tysabri	2	RMS	627	2	DB	SAD	natalizumab 300mg + Avonex	3	0.29		0.23	0.024	0.79		0.06	16.7
Gilenya	1	RRMS	425	2	DB	ARR	fingolimod 0.5mg qd	3	0.24		0.18	0.02	0.75		0.06	16.7
Gilenya	2	RRMS	431	1	DB	ARR	fingolimod 0.5mg qd vs Avonex					0.21				
Aubagio	1	RMS	366	2.2	DB	ARR	teriflunomide 14 mg qd	3	0.27		0.2	0.028	0.74		0.07	14.3
Aubagio	1	RMS	366	2.2	DB	ARR	teriflunomide 7mg qd	3	0.27		0.22	0.084	0.81		0.05	20
Aubagio	2	RMS	370	3.3	DB	ARR	teriflunomide 14mg qd	3	0.2		0.16	0.044	0.8		0.04	25
Aubagio	2	RMS	370	3.3	DB	ARR	teriflunomide 7mg qd	3	0.2		0.21	0.762	1.05		-0.01	-100
Aubagio	3	CIS	214	2	DB	ARR	teriflunomide 14mg qd									
Aubagio	3	CIS	203	2	DB	ARR	teriflunomide 7mg qd									
Aubagio	4	RMS	57	0.75	DB	MRI Lesions	teriflunomide 14mg qd									
Aubagio	4	RMS	61	0.75	DB	MRI Lesions	teriflunomide 7mg qd									
Tecfidera	1	RRMS	410	2	DB	Relapse Free	dimethyl fumarate 240 mg bid	3	0.27		0.16	0.005	0.59		0.11	9.1
Tecfidera	2	RRMS	359	2	DB	ARR	dimethyl fumarate 240 mg bid	3	0.17		0.13	0.25	0.76		0.04	25
Plegridy	1	RMS	512	1	DB	ARR	PEGylated interferon β-1a	3	0.11		0.07	0.0383	0.64		0.04	25
Lemtrada	1	RRMS	426	2	OL	ARR	alemtuzumab vs Rebif 44ug	6		0.21	0.13	0.0084		0.62	0.08	12.5
Lemtrada	2	RRMS	376	2	OL	ARR	alemtuzumab vs Rebif 44µg	6		0.11	0.08	0.22		0.73	0.03	33.3
Zimbryta	301	RMS	919	2.751	DB	ARR	daclizumab 150mg vs. Avonex	3		0.203	0.162	0.1575		0.80	0.04	24.4
Zimbryta	201	RMS	201	1	DB	ARR	daclizumab 150mg	3	0.133		0.059	0.0211	0.44		0.07	13.5
Zimbryta	201	RMS	203	1	DB	ARR	daclizumab 300mg	3	0.133		0.078	0.0905	0.59		0.06	18.2

Table 27 Annualized Relapse Rate As Described in Labels of Approved MS Drugs for RMS

Annualized Relapse Rate As Described in Labels of Approved MS Drugs for RMS														
Drug	Study Number	Type of MS	Treatment Arm Size	Trial Duration in Years	Blinding	Primary Endpoint	Treatment Arm (placebo unless specified)	Annualized Relapse Rate						
								Placebo	Active Comparator	Drug	p-value	Rate Reduction Placebo	Risk Ratio Active Comparator	Absolute Difference
Novantrone	1	RMS	60	2	?	Composite	mitoxantrone 12mg 3 month	0.60		0.20	0.0002	0.66		0.40
Novantrone	2	RMS	21	0.5	OL	MRI	mitoxantrone added to steroids	3.0		0.7	0.003	0.76		2.3
Betaseron	1	RRMS	124	2	DB	ARR	beta interferon 1b	1.31		0.9	0.0001	0.31		0.41
Betaseron	2	SPMS	360	3	DB	SAD	beta interferon 1b	0.63		0.42	0.001	0.33		0.21
Betaseron	3	SPMS	317	3	DB	SAD	beta interferon 1b	0.28		0.16	0.02	0.43		0.12
Betaseron	4	CIS	292	2	DB	ARR	beta interferon 1b							
Avonex	1	RRMS	158	2	DB	SAD	beta interferon 1a	0.82		0.67	0.04	0.18		0.15
Avonex	2	RRMS	193	2	DB	ARR	beta interferon 1a							
Copaxone	1	RRMS	25	2	DB	Relapse Free	glatiramer acetate 20mg	1.2		0.3[Error!]	0.005	0.75		0.9
Copaxone	2	RRMS	125	2	DB	ARR	glatiramer acetate 20mg	1.68		1.19	0.055	0.29		0.49
Copaxone	3	CIS	243	3	DB	Relapse Free	glatiramer acetate 20mg							
Copaxone	4	RRMS	119	0.75	DB	MRI Lesions	glatiramer acetate 20mg						0.34	
Copaxone	5	RRMS	943	1	DB	ARR	glatiramer acetate 40mg	0.505		0.331	0.0001			0.174
Rebif	1	RMS	184	2	DB	ARR	beta interferon 1a 44ug tiw	1.28[77]		0.91[Error!]	0.001	0.29		0.37
Rebif	1	RMS	189	2	DB	ARR	beta interferon 1a 22ug tiw	1.28		0.87	0.0001	0.32		0.41
Rebif	2	RMS	339	1	OL	Relapse Free	beta interferon 1a 44ug vs. Avonex							
Tysabri	1	RMS	627	2	DB	SAD	natalizumab 300mg	0.67		0.22	0.001	0.67		0.45
Tysabri	2	RMS	627	2	DB	SAD	natalizumab 300mg + Avonex	0.75		0.33	0.001	0.56		0.42
Gilenya	1	RRMS	425	2	DB	ARR	fingolimod 0.5mg qd	0.4		0.18	0.001	0.55		0.22
Gilenya	2	RRMS	431	1	DB	ARR	fingolimod 0.5mg qd vs Avonex		0.33	0.16	0.001		0.52	0.17
Aubagio	1	RMS	366	2.2	DB	ARR	teriflunomide 14 mg qd	0.539		0.369	0.0005	0.32		0.17
Aubagio	1	RMS	366	2.2	DB	ARR	teriflunomide 7mg qd	0.539		0.37	0.0002	0.31		0.169
Aubagio	2	RMS	370	3.3	DB	ARR	teriflunomide 14mg qd	0.501		0.319	0.0001	0.36		0.182
Aubagio	2	RMS	370	3.3	DB	ARR	teriflunomide 7mg qd	0.501		0.389	0.0183	0.22		0.112
Aubagio	3	CIS	214	2	DB	ARR	teriflunomide 14mg qd							
Aubagio	3	CIS	203	2	DB	ARR	teriflunomide 7mg qd							
Aubagio	4	RMS	57	0.75	DB	MRI Lesions	teriflunomide 14mg qd							
Aubagio	4	RMS	61	0.75	DB	MRI Lesions	teriflunomide 7mg qd							
Tecfidera	1	RRMS	410	2	DB	Relapse Free	dimethyl fumarate 240 mg bid	0.364		0.172	0.0001	0.53		0.192
Tecfidera	2	RRMS	359	2	DB	ARR	dimethyl fumarate 240 mg bid	0.401		0.224	0.0001	0.44		0.177
Plegridy	1	RMS	512	1	DB	ARR	PEGylated interferon β-1a	0.4		0.26	0.0007	0.35		0.14
Lemtrada	1	RRMS	426	2	OL	ARR	alemtuzumab vs Rebif 44µg		0.52	0.26	0.0001		0.5	0.26
Lemtrada	2	RRMS	376	2	OL	ARR	alemtuzumab vs Rebif 44µg		0.39	0.18	0.0001		0.54	0.21
Zimbryta	301	RMS	919	2.751	DB	ARR	daclizumab 150mg vs. Avonex		0.393	0.216	0.0001		0.45	0.177
Zimbryta	201	RMS	201	1	DB	ARR	daclizumab 150mg	0.458		0.211	0.0001	0.54		0.247
Zimbryta	201	RMS	203	1	DB	ARR	daclizumab 300mg	0.458		0.23	0.0002	0.50		0.228

[77] Calculated as one-half of two-year rate.

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/s/

JOHN R MARLER
05/25/2016