Drug Use Research & Management Program
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New Drug Evaluation: **daclizumab** inj., subcutaneous

Date of Review: January 2017
Generic Name: daclizumab
PDL Class: Multiple Sclerosis

End Date of Literature Search: September 2016
Brand Name (Manufacturer): ZINBRYTA™ (Biogen Inc.)
AMCP Dossier Received: Yes

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:

- How does the efficacy of daclizumab compare with other systemic or biologic therapies for the treatment of relapsing forms of multiple sclerosis (RMS)?
- How does the safety of daclizumab compare with other systemic or biologic therapies for the treatment of RMS?
- Are there any specific subgroups based on demographics in which daclizumab is more efficacious or less harmful than other disease modifying agents for RMS?

Conclusions:

- One 96- to 144-week, phase 3, randomized, active-controlled clinical trial (DECIDE) and one 52-week phase 2, randomized, placebo-controlled trial (SELECT) provide moderate-quality evidence daclizumab 105 mg subcutaneous (SC) every 4 weeks is superior to interferon-beta 1a or to placebo, respectively, for reducing the annualized relapse rate (ARR) (primary endpoint) for patients with relapsing remitting multiple sclerosis (RRMS). For each trial, the daclizumab 150 mg group has a significantly lower ARR than the interferon beta-1a group (45% reduction) and placebo group (54% reduction). For the secondary endpoints, the difference in the proportion of patients who were relapse free between the daclizumab 150 mg and control groups were similar for both studies (~16%, NNT=6). However, the difference was not significant for the DECIDE trial due to controls for multiple comparisons. The mean number of new or newly enlarged T2 hypertensive lesions favored the daclizumab 150 mg group (54% reduction vs interferon and 70% reduction vs placebo), as did the mean total number of new Gd-enhancing lesions 69% reduction vs placebo. Comparisons related to Expanded Disability Status Score (EDSS) (disability progression measure) were not significant.
- Adverse reactions (ADRs) of key interest for daclizumab are hepatotoxicity, cutaneous, and other immune-mediated events, depression/suicide, malignancy, and death. In DECIDE, the daclizumab group vs the interferon beta-1a group had greater incidence of serious hepatotoxicity (0.7% vs 0.4%), serious immune-mediated disorders (4% vs <1%), immune-mediate disorders (32% vs 12%), infection (65% vs 57%), and depression/suicide (10% vs 8%). In SELECT, the daclizumab group vs the placebo group had greater incidence of serious hepatotoxicity (1% vs 0%), immune-mediated disorders (13% vs 7%), infection (50% vs 44%), and depression/suicide (7% vs 2%). Some immune-mediated disorders did not resolve well, and one death occurred. Finally, daclizumab might increase the risk of breast cancer. Across all clinical studies, 0.5% of women and 0.1% of men treated with daclizumab developed breast cancer.

- Because of the serious risks associated with daclizumab, the drug carries a black box warning (BBW) and is contraindicated in patients with a history or evidence of hepatic impairment or disease; LFTs should be performed before and, if indicated, during and after the drug's use; and treatment modifications and specialist referrals made for hepatotoxicity, serious rash, and colitis as indicated. The drug should be avoided in patients with active severe infections, and patients should be tested for tuberculosis and hepatitis B and C. Live vaccinations should be considered before and not during treatment. Daclizumab should be given with caution to those with previous or current depressive disorders and discontinued if severe depressive disorders develop.
- Because the clinical trials are of short duration compared with the chronic nature of multiple sclerosis (MS) and because subjects with history of malignancy, severe allergic reaction, recent serious infection, and abnormal laboratory results indicating significant disease were excluded from the studies, the full extent of adverse effects remains undetermined. Also non-white subjects were underrepresented and older subjects (>55 years) and subjects with greater disability (EDSS >5) were excluded from the trials. Therefore, no or limited data concerning the effectiveness and safety of daclizumab in these subpopulations are available.

Recommendations:

- Designate daclizumab as non-preferred on the Oregon Health Plan fee-for-service practitioner-managed prescription drug plan and limit use to:
  - Adult patients with relapsing forms of MS who have inadequate response to two or more MS disease modifying agents (DMA)
  - Limit prescribing to neurologists or physicians acting in conjunction with a neurologist who is familiar with the use of DMA for MS

Background:

Daclizumab is indicated for adult patients with relapsing forms of MS and, because of its safety profile, should generally be reserved for patients with inadequate response to two or more drugs indicated for MS.[1]

In the United States (US), MS is the most common cause of neurological disability among young adults and affects an estimated 400,000 people. The median onset of MS is about 30 years of age and affects females more than males by a ratio of about 3:1.[2] Both direct and indirect costs rise continuously with each stepwise increase in disability as measured by the Expanded Disability Status Scale (EDSS).[3] In 2011 dollars, the estimated annual direct and indirect healthcare costs for patients with MS ranged from about $9000 to $55,000, with about 77% of total cost attributable to direct cost.[4]

The three major subtypes of MS are relapsing remitting, secondary progressive, and primary progressive. About 85% of patients present with RRMS, which is marked by episodes of worsening or new neurological symptoms followed by periods of inactivity. Most patients with RRMS develop secondary progressive MS about 10 to 20 years after onset of disease, which is characterized by steady neurological decline with few or no clinically recognized relapses. About 15% of patients present with primary progressive MS, which is characterized by steady neurologic decline from onset for at least a year without distinct relapses.[5, 6, 7]

The course of MS is highly unpredictable and varies from person to person. About 15% of patients have a relatively benign course (EDSS≤4, duration >10 years), while about 60% to 70% develop secondary progression.[7, 8]

MS is managed by disease-modifying agents (DMA) and symptomatic and supportive therapies. Approved DMA include five forms of beta interferon, glatiramer acetate, natalizumab, teriflunomide, daclizumab, mitoxantrone, alemtuzumab, fingolimod, and dimethyl fumarate.[5, 9]

The goal of current MS therapy is to prevent relapse, disability progression, and brain and spinal cord injury. Accordingly, among the most important factors clinicians use to select a DMA in clinical practice are disease activity as measured by relapse rate, disability progression, and brain and spinal cord lesion burden on MRI, as well as a drug's potential to cause harm.[7]

In clinical trials, relapse rate most often serves as the primary efficacy endpoint, while disease progression as measured by change in EDSS score and lesion burden serve as secondary efficacy endpoints. The EDSS is based on the results of a neurological examination and the patient's ability to walk and is scored in 0.5 increments from 0, normal neurological examination, to 10, death from MS, with the value 5 corresponding to "ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (eg, work a full day without special provisions)." [10, 11]

US guidelines were developed in 2002 and reaffirmed in 2008 but have not been updated since the introduction of glatiramer acetate and interferon beta products.[5] Canadian 2013 evidence-based guidelines include newer DMAs but were developed before the introduction of teriflunomide, alemtuzumab, and daclizumab to Canada. These guidelines recommend glatiramer acetate or interferon beta-1b as the initial DMA of choice for RRMS patients; should a patient fail or have a contraindication to one, then the patient should be placed on the other. The guidelines further recommend dimethyl fumarate, fingolimod, and natalizumab for patients failing or having contraindications to both glatiramer acetate or interferon beta-1b. Combination therapy is not recommended.[12]

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy: [13, 14, 15]

The FDA's approval of daclizumab for the treatment of patients with RRMS is based on two randomized, double-blind, multicenter, clinical trials:

- DECIDE, a 96- to 144-week, phase 3 trial of daclizumab 150 mg SC every 4 weeks vs interferon beta-1a IM 30 mcg once weekly
- SELECT, a 52-week, phase 2, dose-ranging study of daclizumab 150 mg (approved dose) or 300 mg SC every 4 weeks vs placebo

Both studies enrolled patients who had RRMS were age 18 to 55 years, and had EDSS scores ≤5 at baseline. The two studies differed in their criteria for the number of relapses required for enrollment (see Evidence Table). The primary endpoint for both studies was ARR over the study period, adjusted for baseline relapse rate, EDSS score (≤2.5 vs >2.5) and age (≤35 years vs >35 years), as well as history of interferon beta use (for DECIDE trial). The following were the key secondary endpoints for each study, given in the rank order used for sequential closed testing procedure to control for type 1 error that might result from multiple comparisons:

DECIDE:

1. Adjusted mean number of new or newly enlarged T2 hypertensive lesions over 96 weeks
2. Proportion of patients with confirmed disability progression over 144 weeks, defined as ≥1 point increase from a baseline score of ≥1 or a ≥1.5 increase from a baseline score of 0 on EDSS at 12 weeks
3. Proportion of patients with no relapse at 144 weeks
4. Proportion of patients with an increase from baseline of ≥7.5 points on MSIS-29 Physical Impact score at 96 weeks

SELECT:

1. Mean total number of new gadolinium (Gd)-enhancing lesions on MRI at weeks 8, 12, 16, 20, and 24 in a subset of 307 patients
2. Mean number of new or newly enlarged T2 hypertensive lesions at Week 52
3. Proportion of relapsing patients between baseline and Week 52
4. Quality of life as measured by change from baseline to Week 52 in the MSIS-29 Physical Impact score

The percent reduction in ARR for DECIDE and SELECT were 45% and 54% lower for the daclizumab 150 mg groups (n=919 and 201, respectively) than the interferon beta-1a group (n=922) and placebo group (n=196), respectively ($p<0.0001$ for both comparisons). The difference in the proportion of patients who were relapse free between the daclizumab 150 mg and control groups were similar for both studies (~16%, NNT=6). However, the difference was not significant for the DECIDE trial because the disability progression endpoint was ranked ahead of the relapse endpoint in the sequential closed testing model, and no significance was found for the disability comparison. However, the mean number of new or newly enlarged T2 hypertensive lesions favored the daclizumab 150 mg group for both DECIDE and SELECT: 54% reduction vs interferon and 70% reduction vs placebo, respectively ($p<0.0001$ for both comparisons). Also, the mean total number of new Gd-enhancing lesions, a secondary endpoint only in SELECT, favored daclizumab: 69% reduction vs placebo ($p<0.0001$). Comparisons related to the MSIS-29 Physical Impact subscale were not significant for either study.

Limitation: The studies had several validity concerns, particularly related to external validity. Between the two studies the number of patients in the U.S. was low (13% from U.S. and Canada for DECIDE and none for SELECT). Subjects were predominantly female (67%), Caucasian (92%), and younger (mean age 36). Therefore, efficacy rates may be different for male, non-Caucasian, and older patients. Subjects had EDSS ≤5, efficacy in patients with greater disability unknown, which could perhaps be a population more likely to receive this drug. Drug effectiveness remains unclear because the exclusion criteria in clinical trials were broad and subjective (eg, subjects with history of malignancy, severe allergic reaction, recent serious infection, and significant medical condition in investigator's opinion) and the duration of use of MS drugs is long compared with the duration of the studies. Daclizumab or matching placebo were administered in clinic for DECIDE, whereas prescription is for self-administration, which may affect efficacy in practice. Patients already on an interferon preparation were included and not required to washout before randomization. Also, corticosteroids and glatiramer acetate treatment allowed up to within 30 days before randomization. Therefore, any continuing benefit from these therapies is a potential confounder. The studies do not address the best time to stop or to start drug. Both studies had high attrition rates (21% daclizumab and 25% interferon for DECIDE; 18% daclizumab 150 mg, 19% daclizumab 300 mg, and 17% placebo). Attrition was mostly driven by withdrawal of consent, AEs, and perceived lack of efficacy. EDSS was assessed as a tertiary endpoint in SELECT. DECIDE has missing patient data for hyperintense (14 in INF group and 19 in DAC group) and Gd lesion (13 in the INF group and 19 in DAC group).

Clinical Safety: [1]

The most common adverse reactions from DECIDE, with an incidence ≥2% higher for the daclizumab 150 mg arm (n=919) than the interferon beta-1a arm (n=922) over a median length of treatment of about 27 months, were nasopharyngitis (25% vs 21%), URTI (17% vs 14%), rash (11% vs 4%) influenza (9% vs 6%), dermatitis (9% vs 2%), oropharyngeal pain (8% vs 4%), bronchitis (7% vs 5%), eczema (5% vs 2%), lymphadenopathy (5% vs <1%), tonsillitis (4% vs 2%), and acne (3% vs <1%). The most common adverse reactions from SELECT, with an incidence ≥2% higher for the daclizumab 150 mg arm (n=208) than the placebo arm (n=204) over a median length of treatment of about 11 months, were URTI (9% vs 7%), depression (7% vs 2%), rash 7% vs 3%), pharyngitis (6% vs 4%), increased ALT (5% vs 2%), rhinitis (4% vs 1%), as well as anemia, pyrexia, increased AST, and dermatitis (3% vs <1% each).

Due to the risk of immune-mediated disorders accompanying daclizumab's use, the drug is only available through a REMS program that includes prescriber certification (enrollment and training), pharmacy certification, and patient enrollment and compliance with monitory requirements.

A BBW states daclizumab can cause severe and life-threatening hepatic injury, including autoimmune hepatitis and liver failure that may result in death. Across all clinical studies, 0.3% of daclizumab-treated patients experienced autoimmune hepatitis (with one case of death) and 1% experienced serious hepatotoxicity. In DECIDE, serious hepatotoxicity occurred in 0.7% of the daclizumab group vs 0.4% of the interferon beta-1a, and in SELECT, 1% of the daclizumab group vs no one in the placebo group. Patients taking daclizumab had a greater incidence of ALT or AST elevations >5 X ULN than those taking interferon beta-1a in DECIDE (6% vs 3%, respectively) or placebo in SELECT (4% vs 1%, respectively).

Because of the hepatotoxicity risk, daclizumab is contraindicated in patients who have a history or evidence of hepatic impairment or disease; LFTs should be performed before and, if indicated, during and after the drug's use; treatment modifications and specialist referrals should be made as indicated; and caution should be exercised with those also taking potentially hepatotoxic products.

The BBW also indicates daclizumab increases the risk of immune-mediated disorders, including skin reactions, lymphadenopathy, and non-infectious colitis. Therefore, patients experiencing serious immune-mediated disorder should discontinue the drug and be referred to a specialist. Immune-mediate disorders were experienced by 32% of the daclizumab group vs 12% of the interferon beta-1a group in DECIDE and 13% of the daclizumab group vs 7% of the placebo group in SELECT. Serious immune-mediated disorders were experienced by 4% of the daclizumab group vs <1% of the interferon beta-1a group in DECIDE and 0.5% of both the daclizumab and placebo groups in SELECT. Some immune-mediated disorders did not resolve after drug discontinuation or resulted in invasive diagnostic procedures, hospitalization, or prolonged use of systemic corticosteroids or immunosuppressants. One death occurred due to serious cutaneous reaction. Therefore, serious diffuse or inflammatory rashes should be evaluated by a specialist before continuing daclizumab and discontinuation may be appropriate. Clinicians also should consider sending patients who develop symptoms of colitis to a specialist.

Daclizumab also increases infection risk (65% daclizumab vs 57% interferon group in DECIDE; 50% daclizumab vs 44% placebo groups SELECT) and depression/suicide (10% daclizumab vs 8% interferon group in DECIDE; 7% daclizumab vs 2% placebo group in SELECT). Serious infections occurred in 4% of the daclizumab vs 2% of the interferon group in DECIDE and 3% of the daclizumab vs 0% of the placebo group in SELECT. Depression-related events occurred in and 0.4% of the daclizumab vs 0.7% of the interferon group in DECIDE and no patients in SELECT. Therefore, patients at high risk for tuberculosis should be tested and treated if necessary before initiating daclizumab. Daclizumab should be avoided in patients with other active severe infections until resolution. Patients should be tested for hepatitis B and C. Live vaccinations should be considered before and not during treatment. Daclizumab should be given with caution to those with previous or current depressive disorders and discontinued in those who develop severe depression or suicidal ideation.

In controlled studies, one woman treated with daclizumab vs none treated with interferon beta-1a developed breast cancer. Across all controlled and open-label clinical studies, 8 of 1485 (0.5%) women and 1 of 751 (0.1%) men treated with daclizumab developed breast cancer.

Safety questions:
Because the exclusion criteria in clinical trials were broad and somewhat subjective (eg, subjects with history of malignancy, severe allergic reaction, recent serious infection, and significant medical condition in investigator's opinion) and the duration of use of MS drugs is long compared with the duration of the studies, the full extent of the incidence of ADRs remains undetermined. The extent to which ADR rates reflect the incidence in men, non-Caucasians, older patients (>55 years), and patients with greater disability is unknown, because the study populations were predominantly female, Caucasian, and younger and excluded patients with greater disability (EDSS>5).

Pharmacology and Pharmacokinetic Properties: [1]

Parameter	
Mechanism of Action	Daclizumab's precise mechanism of action MS is unknown, but the drug's mechanism is presumed to involve the modulation of IL-2 mediated activation of lymphocytes via binding to the IL-2 receptor CD25 subunit.
Absorption	Bioavailability is 90% following subcutaneous injection
Distribution and Protein Binding	Vd = 6.34 L; no information available on protein binding
Metabolism	Presumed catabolism to peptides and amino acids
Half-Life	21 days
Elimination	Presumed catabolism to peptides without renal elimination

Abbreviations: Vd = volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Annualized relapse rate
2) Change in Expanded Disability Status Score
3) Lesion burden on MRI
4) Quality of life
5) Safety

Primary Study Endpoint:

1) Adjusted (baseline relapse rate, history INF use, baseline EDSS [≤2.5 v >2.5], baseline age [≤3.5 yr vs >3.5 yr]) annualized relapse rate over study duration. (Relapse = new recurrent neurologic symptoms lasting ≥24 hours)

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1.DECIDE (Study 301) Kappos 2015[14] FDA Med Review[15] Randomized, AC, DB, phase 3 study 244 sites in 28 countries, including the Unites States May 2010 to April 2012	1. DAC SC 150 mg q 4 weeks plus PLA IM q 1 week 2. INF IM 30 mcg q 1 week plus PLA SC q 4 weeks Duration: at least 96 weeks and no more than 144 weeks (median 109 weeks for DAC and 111 weeks for INF)	Demographics: DAC and INF, respectively ·Age (yr): 36, 36 ·Female (%): 68, 68 ·White (%): 90, 90 ·Prior therapy (%): DMD: 41, 41 INF: 34, 34 ·Time since diagnosis (yr): 4, 4 ·Time since 1st symptoms (yr): 7, 7 ·# relapses in ≤1 yr: 1.6, 1.5 ·EDSS (mean): 2.5, 2.5 ·MSIS-29 physical subscale: 22, 22 ·# hyperintense lesions: 52, 49 ·# Gd lesions (mean): 2.3, 2 ·≥1 Gd lesions (%): 46, 44 Key Inclusion Criteria: ·Diagnosed RRMS ·Age 18 to 55 yrs ·MS lesions on MRI ·EDSS 0 to 5 ·≥2 relapses w/in prior 3 yrs, w/ ≥1 w/in yr before randomized *or* ≥1 relapse and ≥1 new lesion w/o relapse w/in prior 2 yrs, w/ ≥1 of events in yr before randomized ·Contraception for of age women	ITT: 1. 919 2. 922 Attrition: 1. 21% 2. 25%	Primary Endpoint: Relapse rate: 1. 0.22 (95% CI: 0.19 to 0.24) 2. 0.39 (95% CI: 0.35 to 0.44) 45% reduction v INF (95% CI, 36 to 53; p<0.0001) Secondary Endpoints in Rank Order: Adjusted mean # new or newly enlarged T_2 lesions over 96 weeks: 1. 4.3 (n=864) (95% CI: 3.9 to 4.8) 2. 9.4 (n=841) (95% CI: 8.5 to 10.5) 54% reduction v INF (95% CI: 47 to 61, p<0.0001) Estimated % patients with disability progression over 144 weeks:† 1. 16 2. 20 HR 0.84 (95% CI, 0.66 to 1.07; NS) Estimated % of patients with no relapse at 144 weeks: 1. 67 2. 51 HR 0.59 (95% CI, 0.5 to 0.69; NS) Est % patients w/ MSIS-29 increase from baseline of ≥7.5 points at 96 weeks: 1. 19 2. 23	NA NA NS* NS* NS*	SAE, excluding MS relapse: 1. 15% 2. 10% Any AE, excluding MS relapse: 1. 91% 2. 91% Treatment d/c due to adverse event, excluding relapse: 1. 14% 2. 9% Hepatobiliary disorder: 1. 3% 2. 2% Serious hepatobiliary disorder: 1. 1% 2. <1% Infection 1. 65% 2. 57% Serious infection 1. 4% 2. 2% Cutaneous event 1. 37% 2. 19% Serious cutaneous event 1. 2% 2. <1%	5/20 0/NA 5/20 1/100 NA 8/13 2/50 18/6 ~1/100	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomization by centralized interactive voice-response system, stratified by study site and before INF use, using permutated-block randomization ·Characteristic well-balanced between study groups Performance Bias: LOW ·Double dummy design ·Patients told to take prophylactic treatment for influenza-like symptoms for the first 4 weeks to reduce potential unblinding due to INF side effects ·All patient and study personnel blinded to treatment assignments Detection Bias: LOW. Patients told to take prophylactic treatment for influenza-like symptoms for the first 4 weeks to reduce potential unblinding due to INF side effects ·All patient and study personnel blinded to treatment assignments Attrition Bias: HIGH. Missing patient data for hyperintense (14 in INF group and 19 in DAC group) and Gd lesion (13 in the INF group and 19 in DAC group) ·High attrition rate (21% DAC and 25% INF). Mostly driven by withdrawal of consent, AEs, and perceived lack of efficacy ·For relapse rate, censoring was at the earliest of start of alternative MS medication, 180 days after the last dose for patients who d/c treatment, or end of treatment for patients who completed treatment Reporting Bias: UNCLEAR. Supported by Biogen and AbbVie Biotherapeutics, including involvement in data analysis and manuscript preparation · Detailed study protocol published **Applicability**: Patient: Broad and somewhat subjective exclusion criteria, so efficacy and ADR rates may not reflect that in clinical practice

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Date: January 2017

		Key Exclusion Criteria: ·History malignancy (skin cancer exclusions), severe allergic reactions, abnormal lab result in investigator's opinion indicates significant disease ·Relapse w/in 50 days before randomization or unstable relapse ·Abnormal blood counts, SrCr, LFTs ·Recent serious infection ·Use of certain immunomodulating therapy regimens		24% reduction in odds of worsening v INF (95% CI, 5 to 40; NS)		Hepatic event 1. 16% 2. 14% Severe hepatic event 1. 1% 2. <1%	2/50 NA	·About 13% of subjects were in the US and Canada ·Subjects had EDSS ≤5, efficacy in patients with greater disability unknown, which could be a population likely to receive this drug ·Subjects were predominantly female, Caucasian, and younger, so efficacy rates may be different for male, non-Caucasian, and older patients. Also, race was determined by the investigator, potentially increasing error in racial assignment. Intervention: DAC or matching PLA administered in clinic during study, whereas prescription is for self-administration, which may affect effectiveness ·Patients already on an interferon preparation were included and not required to washout before randomization. Also, corticosteroids and glatiramer acetate treatment allowed up to within 30 days before randomization. Therefore, any continuing benefit from these therapies is potential confounder ·Study does not address best time to stop or start drug when to start or stop drug Comparator: Active comparator Outcomes: Relapse rate is a surrogate outcome for disability progression. However, it is used because the EDSS has poor sensitivity ·Study of short duration given the high variability of disease progression in terms of disability and length of time to disease progression and given the AE profile Setting: The monitoring frequency is high and highly trained practitioners are required both for MS and for those who experience ADRs

2.SELECT (Study 201) Gold 2013[13] FDA Med Review[15] Randomized, DB, PC, phase 2, dose-ranging study 76 sites in Czech Republic, Germany, Hungry, India, Poland, Ukraine, Turkey, and UK Feb 2008 to May 2010	1. DAC SC 150 mg q 4 weeks 2. DAC SC 300 mg q 4 weeks 3. PLA SC q 4 weeks Duration: 52 weeks (13 doses)	<u>Demographics</u>: ·DAC 150, DAC 300, PLA, respectively ·Age (yr): 35, 35, 37 ·Female (%): 67, 64, 63 ·White (%): 97, 96, 97 ·No previous DMD, except steroid (%): 75, 78, 76 ·Time since diagnosis (yrs): 3, 3, 2 ·Relapses in past yr: 1.4, 1.3, 1.3 EDSS: 2.8, 2.7, 2.7 ·# Gd lesions: 2.1, 1.4, 2 ·≥1 Gd lesions (%): 51, 36, 44 ·# T_2 hyperintense lesions: 45, 36, 40 <u>Key Inclusion Criteria</u>: ·Age 18 to 55 years ·RRMS ·EDSS ≤5 ·≥1 MS relapse in the year before randomized *or* ≥1 new Gd lesions on MRI w/in 6 weeks before randomized <u>Key Exclusion Criteria</u>: ·Severe allergic or reactions or drug hypersensitivity ·History malignancy ·Significant medical condition in investigator's opinion	<u>ITT</u>: 1. 201 2. 203 3. 196 <u>Attrition</u>: 1. 18 2. 19 3. 17	<u>Primary Endpoint</u>: 1. 0.21 (95% CI, 0.16 to 0.29) 54% reduction vs PLA Rate ratio vs PLA 0.46 (95% CI, 0.32 to 0.67; p<0.001) 2. 0.23 (95% CI, 0.17 to 0.31) 50% reduction vs PLA Rate ratio vs PLA 0.50 (95% CI, 35 to 72%; p=0.0002) 3. 0.46 (95% CI: 0.37 to 0.57) <u>Secondary Endpoints in Rank Order</u>: <u>Mean total # Gd lesions at weeks 8, 12, 16, 20, and 24 in a subset of 307 patients</u>: 1. 1.5 (n=101) (95% CI, 1.1 to 2) 69% reduction vs PLA (95% CI, 52.4 to 80.4%; p<0.0001) 2. 1 (n=102) (95% CI, 0.7 to 1.5) 78% reduction vs PLA (95% CI, 66 to 86.4%; p<0.0001) 3. 4.8 (n=104) (95% CI, 3.6 to 6.4) <u>Mean # new or newly enlarged T_2 hyperintense lesions at 52 weeks</u>: 1. 2.4 (n=199) (95% CI, 2 to 3) 70% reduction vs PLA (95% CI, 59.4 to 77.9%; p<0.0001)	NA NA NA NA NA NA	<u>SAE, excluding MS relapse</u> 1. 7% 2. 9% 3. 6% <u>Any AE</u> 1. 73% 2. 76% 3. 79% <u>Death</u> 1. <1%% 2. 0% 3. 0% <u>Serious infection</u> 1. 3% 2. 1% 3. 0% <u>Infection</u> 1. 50% 2. 54% 3. 44% <u>Serious cutaneous events</u> 1. <1% 2. <1% 3. 0% <u>Cutaneous events</u> 1. 18% 2. 22% 3. 13% <u>Other immune-mediated SAE</u> 1. 0% 2. 2% 3. 0% <u>ALT or AST >3X ULN</u> 1. 3% 2. 3%	1/100 3/34 NA NA NA NA 3/34 1/100 6/17 10/10 NA NA 5/20 9/11 NA 2/50 3/34 3/34	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: LOW. Uneven across treatment groups for % of subjects with ≥1 Gd lesions and hyperintense lesions. However, patients on the selected dosage of DAC is the group with more advanced disease ·Randomization by centralized interactive voice response system <u>Performance Bias</u>: LOW. All personnel and patients blinded to treatment assignment, except pharmacist <u>Detection Bias</u>: LOW. All personnel and patients blinded to treatment assignment, except pharmacist <u>Attrition Bias</u>: HIGH. ITT population includes all randomized subjects who received ≥1 dose study drug, except for 21 subjects from a site closed due to misdosing (5 in DAC 300, 8 in DAC 150, and 8 in PLA groups) ·High attrition rate. Mostly driven by withdrawal of consent and AEs for the DAC arms and withdrawal of consent for PLA arm <u>Reporting Bias</u>: UNCLEAR ·Sponsor (Biogen and AbbVie) designed study, held and analyzed data, and participated in data interpretation and manuscript preparation · Detailed study protocol not published **Applicability**: <u>Patient</u>: No subjects in US ·Subjects had EDSS ≤5, efficacy in patients with greater disability unknown, which could be a population likely to receive this drug ·Subjects were predominantly female, Caucasian, and younger. Therefore, efficacy rates may be different for male, non-Caucasian, and older patients. · Broad and subjective exclusion criteria, so efficacy and ADR rates may not reflect what occurs in clinical practice <u>Intervention</u>: Subjects permitted to add INF as a treatment for relapse during the study after Month 6 (n=1 for each DAC group and n=5 in PLA group) <u>Comparator</u>: Nonactive comparator

		·Use of certain immunomodulating therapy regimens		2. 1.7 (n=200) (95% CI: 1.4 to 2.2) 79% reduction vs PLA (95% CI: 71.3 to 84.2%; p<0.0001) 3. 8.1 (n=195) (95% CI: 6.7 to 9.9) <u>% relapsing between baseline and Week 52</u>: 1. 19% HR 0.45 (95% CI, 0.3 to 0.67; p<0.0001) 2. 20% HR 0.49 (95% CI: 0.33 to 0.72; p=0.00032) 3. 36% QOL (change in MSIS-29 physical impact score from baseline to Week 52): 1. -1 (SD 11.8) p = 0.000082 2. 1.4 (SD 13.5) p=0.13 3. 3 (SD 13.5)	NA -17%/6 -16%/7 NS* NS*	3. <1% <u>Injection site reaction</u> 1. 2% 2. 2% 2. 1% <u>Malignancy</u> 1. <1% 2. <1% 3. <1%	 1/100 1/100 NA NA	<u>Outcomes</u>: Relapse rate is a surrogate outcome for disability progression. However, it is used because the EDSS has poor sensitivity. However, EDSS is often assessed as a secondary endpoint. In this study, it was a tertiary endpoint (data not reported here). ·Study of short duration given the high variability disease progression in terms of disability and length of time to disease progression and given the AE profile <u>Setting</u>: The monitoring frequency is high and highly trained practitioners are required both for MS and for those who experience ADRs.

<u>Abbreviations</u> [alphabetical order]: AC = active controlled; ADR=adverse drug reaction; AE=adverse event; ARR = absolute risk reduction; CI = confidence interval; d/c = discontinuation; DAC = daclizumab; DMD: disease modifying drug; EDSS = Expanded Disability Status Score (range from 0 to 10, with higher scores indicating worse disability); hgb = hemoglobin; IM = intramuscular; INF = interferon beta-1a; Gd: gadolinium-enhancing; IM = intramuscular; ITT = intention to treat (patient randomized and received ≥1 dose study drug); LFT = liver function tests; mITT = modified intention to treat; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = 29-item MS Impact Scale (range from 1 to 100, with higher scores indicating a greater physical or psychological effect of MS from the patient's perspective); N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PC = placebo controlled; PLA = placebo; PP = per protocol; q = every; QOL = quality of life; RRMS = relapsing remitting multiple sclerosis; SC = subcutaneous; SAE = serious adverse event; ULN = upper limit of normal; US = United States; WBC = white blood cell count

*NS due to use of sequential closed-testing procedure to control for type I error that could result from multiple comparisons

†Disability progress = ≥1 point increase from baseline score of ≥1 or an increase ≥1.5 from a baseline score of 0 on EDSS at 12 weeks

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	SYRINGE	COPAXONE	GLATIRAMER ACETATE	Y
INTRAMUSC	KIT	AVONEX ADMINISTRATION PACK	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	SYRINGE	REBIF	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	PEN INJCTR	REBIF REBIDOSE	INTERFERON BETA-1A/ALBUMIN	Y
INTRAMUSC	PEN IJ KIT	AVONEX PEN	INTERFERON BETA-1A	Y
INTRAMUSC	SYRINGE	AVONEX	INTERFERON BETA-1A	Y
INTRAMUSC	SYRINGEKIT	AVONEX	INTERFERON BETA-1A	Y
SUB-Q	KIT	BETASERON	INTERFERON BETA-1B	Y
SUB-Q	KIT	EXTAVIA	INTERFERON BETA-1B	Y
INTRAVEN	VIAL	LEMTRADA	ALEMTUZUMAB	N
SUB-Q	SYRINGE	ZINBRYTA	DACLIZUMAB	N
ORAL	TAB ER 12H	AMPYRA	DALFAMPRIDINE	N
ORAL	CAPSULE DR	TECFIDERA	DIMETHYL FUMARATE	N
ORAL	CAPSULE	GILENYA	FINGOLIMOD HCL	N
SUB-Q	SYRINGE	GLATOPA	GLATIRAMER ACETATE	N
INTRAMUSC	PEN INJCTR	AVONEX PEN	INTERFERON BETA-1A	N
SUB-Q	VIAL	EXTAVIA	INTERFERON BETA-1B	N
INTRAVEN	VIAL	MITOXANTRONE HCL	MITOXANTRONE HCL	N
SUB-Q	SYRINGE	PLEGRIDY	PEGINTERFERON BETA-1A	N
SUB-Q	PEN INJCTR	PLEGRIDY PEN	PEGINTERFERON BETA-1A	N
ORAL	TABLET	AUBAGIO	TERIFLUNOMIDE	N

Appendix 2: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZINBRYTA™ safely and effectively. See full prescribing information for ZINBRYTA.

ZINBRYTA (daclizumab) injection, for subcutaneous use
Initial U.S. Approval: 2016

WARNING: HEPATIC INJURY INCLUDING AUTOIMMUNE HEPATITIS and OTHER IMMUNE-MEDIATED DISORDERS
See full prescribing information for complete boxed warning.

Hepatic Injury Including Autoimmune Hepatitis
- **ZINBRYTA can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. Obtain transaminase and bilirubin levels before initiation of ZINBRYTA. Monitor and evaluate transaminase and bilirubin levels monthly and up to 6 months after the last dose (2.3, 2.4, 5.1).**
- **ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment (4, 5.1).**

Other Immune-Mediated Disorders
- **Immune-mediated disorders including skin reactions, lymphadenopathy, non-infectious colitis, and other immune-mediated disorders can occur with ZINBRYTA (5.2).**

These conditions may require treatment with systemic corticosteroids or immunosuppressive medication (5.1, 5.2).

ZINBRYTA is available only through a restricted distribution program called the ZINBRYTA REMS Program (5.3).

INDICATIONS AND USAGE

ZINBRYTA is an interleukin-2 receptor blocking antibody indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of ZINBRYTA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 150 milligrams once monthly (2.1)
- For subcutaneous use only (2.1)
- Train patients in the proper technique for self-administration (2.2)
- Conduct laboratory tests at baseline and at periodic intervals to monitor for early signs of potentially serious adverse reactions (2.3, 2.4).

DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/mL solution in a single-dose prefilled syringe (3)

CONTRAINDICATIONS

- Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN (4)
- History of autoimmune hepatitis or other autoimmune condition involving the liver (4)
- History of hypersensitivity to daclizumab or any other component of the formulation (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Risk of anaphylaxis and angioedema. Discontinue and do not re-start ZINBRYTA if anaphylaxis or other allergic reactions occur (5.4)
- Infections: Increased risk of infections. If serious infection develops, consider withholding ZINBRYTA until infection resolves (5.5)
- Depression and Suicide: Advise patients to immediately report symptoms of depression and/or suicidal ideation to their health care provider. Consider discontinuation if severe depression and/or suicidal ideation occur (5.6)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and ≥2% higher incidence than comparator) reported for ZINBRYTA were nasopharyngitis, upper respiratory tract infection, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema and lymphadenopathy compared with AVONEX; and upper respiratory tract infection, depression, rash, pharyngitis, and increased alanine aminotransferase (ALT) compared with placebo (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Hepatotoxic Drugs: Evaluate potential for increased risk of hepatotoxicity with concomitant use (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2016

Table 2: Adverse Reactions in Adults with RMS with an Incidence at Least 2% More for ZINBRYTA 150 mg SQ Every 4 Weeks than AVONEX 30 mcg IM Once Weekly (Study 1)

Adverse Reaction	ZINBRYTA 150 mg SQ Every 4 Weeks N=919 %	AVONEX 30 mcg IM Once Weekly N=922 %
Nasopharyngitis	25	21
Upper respiratory tract infection [1]	17	14
Rash [2]	11	4
Influenza	9	6
Dermatitis [3]	9	2
Oropharyngeal pain	8	4
Bronchitis	7	5
Eczema [4]	5	2
Lymphadenopathy	5	<1
Tonsillitis	4	2
Acne	3	<1

[1] includes upper respiratory tract infection and viral upper respiratory tract infection
[2] includes erythematous rash, exfoliative rash, macular rash, maculopapular rash, papular rash, pruritic rash, rash, and vesicular rash
[3] includes allergic dermatitis, atopic dermatitis, bullous dermatitis, dermatitis, exfoliative dermatitis, and seborrheic dermatitis
[4] includes dyshidrotic eczema, eczema, and nummular eczema

Table 3: Adverse Reactions in Adults with RMS with an Incidence at Least 2% More for ZINBRYTA 150 mg SQ Every 4 Weeks than Placebo (Study 2)

Adverse Reaction	ZINBRYTA 150 mg SQ Every 4 Weeks N=208 %	Placebo N=204 %
Upper Respiratory Tract Infection	9	7
Depression[1]	7	2
Rash[2]	7	3
Pharyngitis	6	4
Increased ALT	5	2
Rhinitis	4	1
Anemia	3	<1
Pyrexia	3	<1
Increased AST	3	<1
Dermatitis[3]	3	<1

[1] includes depressed mood and depression
[2] includes erythematous rash, exfoliative rash, macular rash, maculopapular rash, papular rash, pruritic rash, rash, and vesicular rash
[3] includes allergic dermatitis, atopic dermatitis, bullous dermatitis, dermatitis, exfoliative dermatitis, and seborrheic dermatitis

Appendix 3: Proposed Prior Authorization Criteria

TBD